ON CHOLECYSTOGENIC ACUTE HEPATITIS

By

HJALMAR ÅGERUP

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From the Surgical Department (Chief: S. Richter, M. D.) of Sundsvall Hospital, Sundsvall, the Surgical Clinic (Chief: Professor O. Hultén) of the University Hospital, Uppsala, and the Department of Histology (Chief: Professor M. Wrete), University of Uppsala, Uppsala.

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Preface.

The investigations whereon the present publication is based were commenced as early as 1942. At that time I served at the surgical department of Sundsvalls Hospital. It was the Surgeon-in-chief, Doctor Sölve Richter, who had the generosity of giving me the idea of finding the anatomic basis of the here presented clinical observations concerning the existence of liver involvement in gallstone diseases. I wish to convey my most sincere thanks to Doctor Richter for his suggestion and for his advice and encouragement during the first stages of the investigation.

The latter part of the study was performed at the Surgical Clinic of the University Hospital, Uppsala. To the chief of that clinic, Professor Olle Hultén, who has interested himself in my work and given me sound advice on various problems as they cropped up, I should like to offer my heartiest thanks.

The histotechnical portion of the investigation was carried out at the department of Histology, Uppsala. Professor Martin Wrete, its head, has in many ways facilitated my work and accorded the problem much valuable attention in friendly discussions. I am most deeply indebted to him for this.

I have had the advantage of having the patho-anatomic findings confirmed by the Professor of Pathology to the University of Uppsala, Nils Gellerstedt. His rich experience has come also to my benefit when I evaluated my observations, thereby sparing me much tedious work. For his kindness in all respects I owe him my deep and lasting gratitude.

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Hjalmar Ågerup.

Introduction.

Any clinician with experience has probably noticed that some patients with biliary calculus have symptoms, usually in the form of a slight icteric discolouration of the sclerae, which cannot at a later operation be attributed to any visible changes in those parts of the biliary ducts that can be observed from the incision through the abdominal wall. In such cases it has been surmised that the changes must affect intrahepatic portions of the biliary ducts, i.e. the patient must have had cholangitis or a temporary swelling of the duodenal papilla. Others have found a swelling of the liver and have envisaged some form of hepatic inflammation. That has set off a debate with opinion against opinion. The literature has then been consulted for some shred of information that might clear up the matter, but to no avail. The changes are neither severe no fatal; they are comparatively moderate and transient, and therefore they seldom come under the pathologist's expert eye. In a very limited number of cases, attempts have been made to solve the problem whether the liver is affected in an attack of cholelithiasis, by excising samples from the liver, in connection with an operation and examining them through the microscope. However, the few observations made have given rise to far-reaching, and therefore unreliable and often contradictory, conclusions.

Therefore, in the present paper, I shall attempt to describe, on the basis of a fairly large series of samples from the liver of patients with gallbladder affections, the hepatic changes that might underlie the observed clinical symptoms of liver affections, secondary to gallbladder disorders. The person who tackles an investigation of this nature must, in order to get results, strictly limit his objectives; in the present paper I shall therefore merely discuss *the acute changes seen in the liver in immediate connection with an isolated attack of cholelithiasis as it is manifested by clinical symptoms*. A separate chapter describes the microscopical structure of the liver and the intrahepatic circulation. In this connection the routes by which the toxins may affect the liver are discussed. General factors, that may be of importance for the genesis of hepatic damage, will be discussed subsequently. Thereafter the liver changes relevant to some factors of an acute attack of cholelithiasis will be treated. Finally some clinical signs that may be related to the changes in the liver associated with an acute attack of cholelithiasis will be dealt with.

CHAPTER I.

Review of Literature.

a. Earlier Treatises on Liver Changes associated with Cholecystitis.

That the liver is co-affected in disorders of the gallbladder is old knowledge. As early as 1888, RIEDEL called our attention to the enlargement of the liver often associated with disorders of the gallbladder. He considered this enlargement to be most pronounced within the tongue-shaped process of the liver extending downwards between the gallbladder and the falciform ligament, and which since has been known by the name Riedel's process or lobe. Actually, Riedel could by means of clinical palpation feel that the liver was enlarged in 24 of 42 cases of cholelithiasis. Further statements concerning enlargement of the liver in association with attacks of cholelithiasis have been reported by CHARCOT, NAUNYN (1892), QUINCKE (1903), ROLLESTON (1912) and KEHR (1913).

In 1917, REIMANN was the first who by histological methods revealed that in cholecystitis inflammatory changes are exhibited by the parenchymatous bed of the gallbladder. GRAHAM (1918) later became the investigator who, during a succession of years, devoted the most interest to hepatitis as a constant phenomenon accompanying cholecystitic conditious. He based his opinion on 30 sample sections taken at operation from the right lobe of the liver at varying distances from the gallbladder. Basing his opinions on this series, he held that:

"1. In cases of acute or subacute cholecystitis there has been constantly found in the liver microscopical evidense of inflammation.

2. The hepatic inflammation is characterized by leucocytic infiltration of the intorlobular or periportal sheaths, in the more severe types of inflammation the infiltration may involve also parenchyma at the peripheries of the lobules and be associated with more or less oedema, slight necrosis, and moderate fat infiltration.

3. Cultures from both the liver tissue and from the bile in the gallbladder have usually revealed the same organism from each of the two different sources.

4. In chronic cholecystitis the liver microscopically often presents a picture practically identical with that of an early case of cirrhosis.

5. The inflammatory reaction appears to be chiefly a pericholangitis.

6. The gross enlargement of the liver is probably usually due chiefly to oedema."

In 1924, TIETZE & WINKLER (Breslau) published results from 50 samples excised from the liver of persons with gallbladder disease. They

found the same changes in the liver as GRAHAM but they also discussed two groups of lesions which are characterized by extensive parenchymatous damage. No other author has reported the same kind of parenchymatous damage. The American HEYD (1924) described 18 cases of gallstone disease with liver damage. The Kiew surgeon GENKIN (1927) published 15 cases of chronic cholecystitis without stone and found periportal infiltrates in the liver. KOSTER, GOLDZIEHER, & COLLENS (1930, New York) studied the liver in 27 cases of chronic cholecystitis and found lymphocyte infiltrates round the branches of the portal vein and the small bile ducts. Their countrymen JUDD, NICKEL, & WELLBROCK (1932) made similar observations in the livers from 37 persons with gallbladder affection. The Englishman FLINT (1930) described histologic liver changes in 20 cases of pathologic gallbladder, finding that the interstitial hepatitis was more pronounced than in 14 cases of normal gallbladder. In Italy, PETTINARI (1932, 1939) had published over 40 cases of cholecystitis and had found liver changes of varying degree and extent. He had found phlegmonous liver changes, sometimes combined with purulent cholangiolitis, but more commonly the interstitial hepatitis mentioned above. In some cases he observed also parenchymal degeneration.

About a dozen years ago, however, liver biopsy had become increasingly common owing to the advent of the puncture method; and the improvements introduced by IVERSEN & ROHOLM (1939) made the technique even more widely accepted. Specimens were still excised in connection with operations, but the predominant method was to puncture the liver. This new method made it easier to obtain large series, and the most varying forms of hepatic disorders could now be subjected to histologic study. Still, most investigators have given their attention to infectious hepatitis, since repeated punctures made it possible to discover the disorder at an early stage and follow its development until it gradually entered the final phase. The method made it possible, moreover, at biopsy to distinguish between different predominantly icteric conditions.

By 1948, 2 500 needle biopsies had been reported. The method has without doubt great advantages and it has been the implement leading to many valuable findings concerning pathology in some stages of various morbid hepatic conditions. However, it permits but a narrow piece of the liver tissue to be examined, orientation thereby becoming most difficult. Diffuse forms of parenchymatous liver damage are therefore best suited for study by this method. IVERSEN & ROHOLM studied thus the pathology of infectious hepatitis. Serial investigations into the development of cirrhosis of the liver have been made by KRARUP & ROHOLM (1941). GILLMAN & GILLMAN (1946) have reported valuable observations with respect to liver disorders due to nutritional disturb-

ances. The method has also been useful in the diagnosis of abscesses complicating amebic dysentery.

The puncture method is not without its hazards, and different authors have reported an average mortality of 1 per cent, predominantly owing to hemorrhages which usually affect emaciated patients. Specimens are still used, however, and they must be considered superior since they can be taken from any part of the liver, seen with the naked eye to represent average conditions or to be particularly interesting. By excision a much larger contiguous piece of the organ can be obtained so that the localization and extent of the changes, if any, can be more precisely determined. With such knowledge available, it may later or in another case be possible better to interpret what is seen in a piece of liver tissue extracted by needle biopsy. Furthermore, it has been shown that there is no risk of complications following excision of tissue specimens. In a comprehensive study by Popper & Franklin (1948), a combination was used of specimen excision and needle biopsy, the result being a division of liver lesions into medical and surgical lesions. The article reviews our present knowledge of the scope of biopsy and will therefore be summarized here.

The medical form of liver lesion includes hepatitis and cirrhosis, caused by primary lesioning of the liver parenchyma; whereas the surgical type comprises liver lesions secondary to tumours, calculi or strictures. It is typical of the medical form that hepatocellular dysfunction affects the biliary system, and of the surgical form that cholecystic disorders influence hepatocellular function. Thus, since both forms fully developed involve hepatocellular function as well as the biliary system, the only means of determining the type of disease a patient suffers from is biopsy at an early stage. They had made some autopsical examinations, but they stressed that the biopsy specimens taken shortly before death and the autopsy specimens taken shortly after death showed, when compared, that marked histologic changes rapidly set in after death. Consequently, specimens taken at autopsy are not equally valuable for observation of liver changes. Hepatitis of the primary type was divided into an infectious form caused by virus and a toxic form caused by a wealth of etiologic factors. Secondary (surgical) hepatitis was divided into a biliary and a purulent form.

It will be shown in the present paper that there exists a toxic variety of surgical hepatitis, cholecystogenic hepatitis. I shall, therefore, briefly review the pathoanatomy of the toxic form of medical hepatitis as well as that of surgical hepatitis (Popper & Franklin).

Toxic hepatitis is caused by various chemical (e.g. arsenic, cinchophen), bacterial (e.g. pneumonia) or endogenous (e.g. hyperthyroidism) toxins or unknown harmful agents. The disorder is attended by more or less serious damage to the liver cells, in the form of coagulation necrosis and partial cellular hyalinization. Fatty changes are often present,

and in 3 cases (of 21) of so dominating nature as to justify the term diffuse fatty liver. The parenchymal lesions were slightly accentuated towards the centre. The mesenchymal reaction, if any, was subordinate. The mobilization of Kupffer cells and macrophages was not so pronounced as in the virus form. Sometimes, however, a number of neutrophils could be distinctly observed. In fatal cases, neither central nor peripheral necrosis was particularly rare, and the gradual destruction of cells with presence of cellular fragments without nuclei was characteristic. In cases of intrahepatic "biliary obstruction," the number of bile casts appeared out of proportion to the cellular damage. There was only little proliferation of the bile ducts.

Biliary hepatitis (73 cases). The degree of the hepatitis depends on the duration and degree of the biliary obstruction, and is therefore much higher in association with malignant tumours and strictures, the obstruction then usually being total, than when caused by biliary calculi.

A histological inspection of bile casts and the intracellular bile granula (mainly the central lobular zone) indicated bile stasis proportional to the degree of liver damage, particularly in the early stages. However, every slide inspected revealed some liver cell damage in, chiefly, the central portion of the lobule. In later stages, "bile casts" were visible also in the periphery, while the intermediary zone was free. Large areas of diffusely necrotized liver cells with bile imbibition (biliary infarction) sometimes occurred. The mesenchymal reaction was subdued. Polymorphonucleated leukocytes were rare except in small focal necrotic areas in cholelithiasis. Periportal infiltration was subordinate. The Kupffer cells were proliferated and charged with bile pigment. The periportal areas exhibited a moderate degree of infiltration of the biliary canals and, in the protracted cases, there was often marked periportal, concentric fibrosis which was sharply marked off from adjacent parenchymal tissue. As the process continued, the lobular spaces around the periportal areas became larger and the picture was similar to that in biliary or obstructive cirrhosis.

Purulent hepatitis (15 cases) is caused by bacterial infection of the portal triad. Apparently the bacteria have passed from the portal system through the walls of the liver sinusoids into the perisinusiod tissue spaces, and then on to the terminal lymphatics that mainly are located in the portal triad. A perilymphatic, inflammatory process then commences which may attack the biliary canals from outside. The infection less frequently comes by way of the lumen of the biliary canals. Serious perilymphangitis, which may deteriorate into frank suppuration, is independent of the duration or degree of obstruction, and may occur without obstruction. The disorder is more likely due to inflammatory processes in the portal system, particularly of the type associated with cholelithiasis. The series comprised 11 cases of cholelithiasis, 2 of pan-

creatic carcinoma, 1 of duodenal ulcer and 1 of cancer of the stomach. There was not necessarily pronounced jaundice. Clinical symptoms of bacteremia, e.g. chills, fever and leukocytosis, however, are often present. The histologically most important feature was an inflammatory infiltration of the periportal spaces. Polymorphonucleated leukocytes were common. The biliary canals exhibited definite proliferation, chiefly of mature character. The leukocyte infiltration was often extensive along the proliferated biliary canals, and it was localized especially around the lymphatics in the greater portal triad. The liver parenchyma exhibited more or less diffuse hepatocellular damage and necrotized foci which could be fairly extensive. The degree of biliary stasis varied from case to case. In later stages the picture may be very similar to that in what is here called infectious cirrhosis.

In addition to the changes in the liver in gallstone disease described above, Mateer, Hartman, Baltz, Fallis, McGraw, & Steele (1948) have described another form not seen earlier of liver damage, which they termed acute infiltrative hepatitis. It is characterized by 1) absence of necrotic areas and disintegrated cells in the parenchyma and 2) presence in the parenchyma of slight, moderate or severe infiltration with polymorphonucleated cells. The latter cells are usually arranged in a circle around the central vein in the lobule, although they may be dispersed all over the parenchyma. Some of the polymorphonucleated cells were seen inside the parenchymal cells and others were apparently extracellular. This form of hepatitis was seen in 15 per cent of 132 cases of cholelithiasis and in 10 per cent of 31 cases of peptic ulcer. As regards the origin of this form of hepatitis, it is probable that it is secondary to infection or inflammation in the wall of the gallbladder.

The liver changes described above, all of which have been found in conjunction with affections of the biliary passages, have given rise to numerous speculations concerning their etiology. The central question has then been whether the hepatitic changes are primary or secondary to cholecystitis. Graham, who was the first to take up the matter, surmised that the infection of the liver came first, then microbes coming from the liver via the lymphatics of the biliary ducts infected the gallbladder, first the outer layers and last the mucosa. This view was borne out by Judd & Peterman. Like Graham, Pettinari and others they suggested that the liver was infected via the portal vein, the main cause of infection being of appendicitic origin. (Cf. Chiary & Pavel, Heyd, Killian & Mac Need, etc.) Graham sticks to the same view also in later works, in which he says that this route of infection is usual in cholecystitis, but he also thought that other routes were possible, viz. by direct hematogenous infection of the gallbladder. In such cases the bacteria were said to reach the gallbladder via the circulating blood, and bacterial emboli in the capillaries of the gallbladder might give rise to inflammatory processes. Another possibility might be contact infection

from the liver bile, or infection ascending from the choledochus and duodenum. In proof of his basic theory, GRAHAM stated that cultures from the liver and gallbladder produced the same bacteria.

The experimental investigations into this problem performed by WILKIE (1928) are most interesting. They all suggsted a hematogenic origin of the infection of cholecystitis and a lymphogenic genesis of hepatitis, which in his view was secondary to cholecystitis. WILKIE injected intravenously in rabbits streptococci isolated from the regional lymph nodes of the gallbladder in persons operated on for cholecystitis. This resulted in both cholecystitis and hepatitis, but if before the injection he introduced an omentum flap between the liver and gallbladder only cholecystitis set in. This also was the case if the cystic duct was ligated before the injection.

KOSTER, GOLDZIEHER, & COLLENS (1930) made the same observations as GRAHAM, i.e. that cholecystitis and hepatitis go together, but they thought that cholecystitis came before the liver changes, which is in agreement with WILKIE's experiments. They maintained that the bacteria come to the gallbladder after passing the liver barrier without leaving any significant local changes, and that the infection then spreads from the inflamed gallbladder via the lymphatics to the liver, causing hepatitis. They considered their assumption to bear out the clinically severer liver symptoms observed after repeated attacks of cholecystitis. As evidence that the lymph passes from the gallbladder to the liver and not vice versa, they emphasized the work by HARER, HAGIS, & VAN METER (1922) on the direction of the lymph stream between the gallbladder and the liver. The latter authors found that, if potassium rhodanide solution was injected into the gallbladder, iron chloride produced a rhodanide reaction in the lymph obtained by inserting small capillary tubes through the serous membrane of the liver.

JUDD, NICKEL & WELLBROCK (1932) isolated from gallbladder and liver, bacteria which they injected intravenously into rabbits. They found that, among the bacteria cultured in this manner, streptococci possessed a degree of selective affinity to the liver, which did not apply to the other forms of bacteria (staphylococci, diphtheroid organisms and bacilli). They were able to prove that cholecystitis regularly is attended by hepatitic changes which, however, are not necessarily proportional to the gallbladder changes. The hepatitis was perhaps secondary to an infection in the portal region and had been caused as a reaction on the part of the liver of its detoxification of bacteria or toxins coming to it from the portal region. They were certain that hepatitis can be present primarily and might give rise to cholecystitis. Removal of the gallbladder, therefore, should not stop the hepatitic symptoms. They found a proportionality between the number of bacteria in the liver and the degree of hepatitis but were unable to demonstrate the causal relationship.

On the basis of samples excised from the liver in cholecystitis, Pettinari (1932, 1939) assumed that the biliary ducts are infected from the blood pathways and that cholecystitis often is preceded by intrahepatic cholangitis.

La Manna (1936—37), having particularly interested himself in the pathogenesis of cholangitis, studied a large series of autopsy material and found that cholangitis is more common in the large biliary ducts; that its appearance in different sections of the biliary tree indicates that the infection is of longest standing in the greater branches and most recent in the smaller. This fact he considered suggestive of an ascending infection and not of hematogenous cholangitis. However, he did not think that the investigation contraindicated that bacteria are capable of passing through the walls of the biliary canals, but that in most cases this process does not lead to inflammation. He also warned against confusing cholangitis and interstitial hepatitis which is characterized by infiltration of small cells (Virschow's lymphoma) in the portal cords. He pointed out that such infiltrates are found in many toxic-infectious disorders (cf. Rössle, Lubarsch, Siegmund, Syssek, Kahlsdorf, Sternberg, Wagner, Kettler, Fraenkel, etc.) and are therefore typical not only of cholecystitis. These infiltrates appear irrespective of the type, degree and duration of the toxic action in the different morbid conditions. Most often they surround the vessels and biliary canals in Glisson's capsule. The localization around the biliary canals has often given rise to the faulty diagnosis "pericholangitic foci." The infiltrations may be interpreted as signs of the detoxifying function of the liver, the toxins being eliminated through the lymphatics (Rössle). An accumulation of leukocytes around the biliary canals is, according to La Manna, not typical of pericholangitis, particularly not if the slides are taken from peripheral sections of the liver which contain every type of physiologic involution. Thereby he condemned samples from the liver exciseable at operation. La Manna also rejected the clinical diagnosis of cholangitis, his opinion being that all too often it is based on observations of bacteria in the bile, doudenal juice, blood or merely on clinical symptoms, which most often have been confirmed inadequately by uncertain anatomical findings. He stated that only the clinician can produce evidence of dysfunction in the liver or biliary canals without having to provide a morphologic basis for the pathologic process.

Attempting to summarize our present knowledge concerning the inflammatory changes in the liver observed in association with gallbladder inflammations, I may say that the observations are in fair agreement, especially in regard to the coexistence of interstitial hepatitis and cholecystitis. Some authors have, moreover, observed degenerative changes also within the liver parenchyma. Clinicians, who chiefly have made their observations on samples excised from the liver at ope-

ration, are practically unanimous in asserting that cholecystitis and interstitial hepatitis go together. Pathologists, who have better means thoroughly examining the whole liver but not as histologically intact material, have made similar observations. The latter, however, have a wider view on the problem and emphasize the multiform importance of interstitial hepatitis, pointing out that it may occur in many infections in the body other than cholecystitis. The concept "cholangitis or pericholangitis," so beloved by clinicians, is mostly contradicted by pathologists who must have damage, chiefly, to the epithelium in the biliary canals before they speak of cholangitis; and who doubt that the desease by clinicicans so often interpreted as cholangitis, have any relation whatsoever with an inflammatory process in the biliary canals. They are of the opinion that cholangitis in the pathoanatomical sense of the term exists only in a very small minority of cases. Pathologists also maintain that the samples excisted at operation have a very limited value for estimations of the condition of the liver. When, nevertheless, I have the temerity to present my findings from samples excised from the liver at gallbladder operations, it is because I wish to make known the clinical points of view and problems, and because I think clinicians regard the bile problem not in the same light as pathologists. I have, moreover, in my investigations found a form of hepatitis that probably does not become manifest in material taken at autopsy, at least not as plainly as in the fresh material I have had at my disposal.

b. The Development of Cholecystitis.

Before commencing to describe more closely my investigations, I must briefly discuss a problem that is intimately related to the changes in the liver associated with cholecystitis, viz. the etiology of cholecystitis: whether it is bacterial-infectious, mechanical or chemical.

The etiology commonly held — that which appears in current textbooks — is bacterial. A glance at the literature reveals that 9 out of 10 publications give bacterial infection as the most probable cause of cholecystitis. Andrews & Magner have investigated the contents of operatively extirpated gallbladders, finding that in 65 per cent of the cases it contained sterile bile. The corresponding figure arrived at by Osler was 52 per cent. In opposition to these reports, Huntemüller stated that he obtained 100 per cent positive bacterial growth in combined cultures from the gallbladder wall and liver. However, his culture method has been criticized by Schultze who has pointed out its great inherent risk of contamination. According to the most reliable investigations into the bacterial content of the gallbladder in cholecystitis, infection can be demonstrated in cultures from 1/3—1/2 the cases. The bacteria most frequently present belong to the coli group (50 per cent), next in order of frequency are streptococci, then come typhoid and

paratyphoid bacilli and last staphylococci. According to Meyer & Löwenberg, the streptococci most often are enterococci, because streptococci cannot grow on a substrate containing more than 10 per cent bile. Apparently, therefore, the most common bacteria are those found in the bacterial flora of the intestines.

A enormous number of investigations have been performed to put to the test the development of cholecystitis from bacterial infection. Many authors have by means of animal experiments attempted to prove their clinical observations. A popular method has been intravenous injection of bacteria. Using this method Blackstein found typhoid bacilli in the bile several days or weeks after the injection. Sherrington used B. anthracis and B. pyocyaneus and staphylococci, but recovered them in the gallbladder in only 16 of 49 cases. Many authors have introduced the bacilli directly into the wall and cavity of the gallbladder. In these cases the results were more conflicting. Rosenow pursuing his hypothesis concerning a specific affinity of bacteria (especially streptococci and coli) to certain organs and tissues, attempted to establish a relationship between infectious foci and gallbladder disease. He employed intravenous and direct inoculation and obtained contradictory results. Meyer & coworkers, using typhoid bacilli and both methods, obtained positive results. Doerr observed that the excretion of typhoid bacilli in the bile, which took place regularly when they had been injected into the venous system, vould be prevented by ligating the cystic duct. However, Kock & Chiarolanza obtained follwing intravenous injection, the opposite result and found typhoid bacilli in the gallbladder even after the cystic duct had been ligated. In connection with Rosenow's hypothesis concerning specific affinity of the bacteria to certain tissues, Brown's work should be noted. In emulsified gallbladder tissue from human subjects with cholecystitis he chiefly found streptococci, which he injected into rabbits and thereby serologically proved the microorganisms to possess direct etiologic importance and specific affinity to the gallbladder. Staphylococci were used in experimental studies by Magner & Hutcheson, who produced lesions in the wall of the gallbladder by injecting them beneath the serous membrane, whereas the same lesions appeared in a limited number of cases when the injection was made into the cavity of the gallbladder.

It will be noted that these attempts to produce experimental cholecystitis by means of bacteria produced varying and often contradictory results. This may in part be due to differences in technique. Puncture is often complicated by inflammation around the hole, which makes interpretation more difficult. The quantities of bacteria injected are so large that no similar bacteriemia is likely when the gallbladder is infected from some focus of infection. Many authors state that the liver is a very effective filter of bacteria and none can reach the bile unless they are injected in enormous quantities.

In comparison to the enormous extent of the literature on cholecystitis as caused by bacterial infection, relatively little is known of chemical cholecystitis. MANN induced acute lesions in the wall of the gallbladder by injecting Dakin's solution intravenously. In other experiments, changes in the wall of the gallbladder were caused by direct introduction of chemical or mechanical irritants such as mustard oil (DARENBACHER & SACKS). Also irradiation with roentgen rays turned out to cause acute inflammatory changes in the gallbladder (BRAMS & DARENBACHER).

A problem that in recent decades has attracted increasing attention is whether the juices normally occurring in the bile ducts are capable of damaging the ducts to such an extent that cholecystitic changes can appear (WOLFER, WOMACK & BRICKER, etc.). The fluids in question are the bile and the pancreatic juice. Since in a large number of cases the pancreatic duct opens into the bile duct above the papilla, the pancreatic juice may possibly enter the bile canals. According to the latest figures by HJORT (1947), there is a common outlet in 86 per cent of the cases and it is visible on a cholangiogram in 46.7 per cent. In these cases, therefore, pancreatic juice and bile would be mixed in the choledochus and if for some reason — calculus, spasm, papillitis — the papilla Vateri should be closed, the distribution of the two juices would depend on the secretory pressure in the respective glands, provided that there was no spare outlet in the form of an accessory pancreatic duct. According to HJORT's figures, 14 per cent of all men and 44 per cent of all women have such an accessory duct. Since, however, the secretory pressure in the pancreas is greater than the maximum pressure in the contracted gallbladder (IVY), there must in a certain percentage (greater for women than for men), be a means for the pancreatic juice to enter the bile ducts. Moreover, it has been shown experimentally that India ink introduced into the lower reaches of the choledochus can be demonstrated in the gallbladder. COLP, GEBER, & DOUBILET stated that they demonstrated the presence of amylase and trypsin in the gallbladder in 2 of 3 examined cases of acute cholecystitis. Experiments have shown that under different conditions the pancreatic juice is capable of attacking the wall of the gallbladder, causing various types of changes from acute necrosis to chronic hyperplastic or inflammatory reaction. However, in order to lesion the gallbladder in this manner, the pancreatic juice must be activated (LOMBARDI, DRAGSTEDT). Pure bile does not activate trypsin (DOUBILET). On the other hand, IVY has found that there is a violent reaction in the mucosa of the gallbladder after introduction of 15 cc tenth-normal sodium bicarbonate solution. Pancreatic juice having the same alkalinity as this solution, it is possible that the alkaline pancreatic juice coming into the gallbladder may cause chemical irritation of its mucosa with cellular destruction and that the products of decomposition activate the enzyme (LOMBARDI). Fairly comprehen-

sive investigations into the importance of pancreatic juice for the development of cholecystitic changes in the gallbladder have been performed by HJORT. That the alkaline pancreatic juice does not equally attack the choledochus and the gallbladder has been attributed to the capacity of the latter constantly to resist the alkaline liver bile.

The second factor that might play a role in the etiology of cholecystitis is the bile itself. It is known that in the gallbladder the bile from the hepatic duct is concentrated, often as much as 10 times, while simultaneously the proportions between the components change so that the bile acids predominantly are concentrated and, according to HAMMARSTEN, attain a concentration of 10 per cent. Bile solutions of the same strength have proved strongly toxic to tissues (peritoneum, muscle, pancreas). WOMACK & BRICKER demonstrated experimentally that a slight subacute reaction or slight fibrosis may develop in the gallbladder if, when filled with normal gallbladder bile, it was ligated at the cystic duct. If they concentrated the bile to double strength, the gallbladder, which had been ligated at the cystic duct, became severely lesioned when exposed to such contents. The changes consisted of edemas, hemorrhages och gangrene but only slight leukocyte infiltration. FLEXNER has shown that the toxic constituents of the bile are the bile salts. BAYER demonstrated that even very dilute serum proteins contain protecting substances that neutralize the toxic effect of bile.

It has been proved by ARONSON & ANDREWS that if pure bile salts of the same concentration as in normal bile are introduced into the gallbladder the result will be a distinct toxic effect and it was remarkable that the reaction in the wall of the gallbladder was the same as that seen in acute cholecystitis in man. The microscopic pattern agreed with that of acute cholecystitis. Sodium desoxycholate proved to be the most toxic fraction in the bile, and in a solution as weak as 7.5 per cent it yielded a distinct reaction.

A number of authors have looked for yet other causative factors in cholecystitis. DENTON for example, assumed that there exist mechanical and circulatory causes of pathologic conditions in the gallbladder. He stated that an encysted calculus in the gallbladder might cause circulatory disorders and a picture similar to cholecystitis. FEINBLATT maintained that the metabolism of cholesterol, which is the basis for strawberry gallbladder, was distrubed. BOYD held that infection is the cause of this metabolic disorder, and in cases of strawberry gallbladder WILKIE & ROSENOW obtained positive cultures from the wall, contents and calculi.

Most probably the cause of cholecystitis is not a single one of these etiologic factors but a combination of several of them. Sometimes one factor predominates, sometimes another. One factor, however, seems to recur fairly regularly and that is the element of stasis. The stasis may either be due to an obstruction that prevents free flow of bile into the intestine or to a deficiency in the voiding mechanism of the gall-

bladder. Normally, the voiding pressure of the gallbladder is by no means great. In dogs it has been measured and is at most 20—25 cm water column (Ivy). Merely a slight edema in the wall or slight fibrosis, or according to some authors adherence to adjacent tissues, may be sufficient to give rise to incomplete voiding and therefore retention. It must be kept in mind, moreover, that the motility of the gallbladder is strongly dependent on conditions in the duodenum. An alkaline reaction to the contents of the duodenum lessens the tone of the gallbladder musculature, whereas its contractility is increased by an acid contents. The gallbladder is emptied physiologically by contraction together with simultaneous slackening of the sphincter of Oddi. This mechanism is released by cholecystokinin, a hormone produced in the mucosa of the upper intestine, when the mucosa comes into contact with fat or partly digested proteins. When this reaction is weakened, the tone of the gallbladder is lessened and a measure of stasis caused.

CHAPTER II.

The Material.

a. General.

The present study has been confined to acute and chronic cholecystitis and cholelithiasis. It is based on 370 cases, 3/4 of them being cholecystitis. The cases have been divided into 3 main groups: acute and chronic cholecystitis and cholelithiasis, the classification being clinical and not pathoanatomical. Since acute cholecystitis often is associated with chronic changes in the gallbladder, the classification was not simple (cf. p. 211). All patients with distinct clinical symptoms and macroscopic anatomical changes suggestive of acute inflammation were grouped under acute cholecystitis, even if the gallbladder exhibited marked chronic changes in the wall and mucous membrane. In order to avoid too small groups, all cases of acute inflammation were grouped together, although the degree of the inflammatory process varied within wide limits. As the operation was performed at very different stages of the inflammation, it would have been very difficult on the basis of the appearance of the gallbladder to make a strict classification according to the stage of the inflammation at the time of operation. Cases of acute edema in the wall of the gallbladder with surface fibrinization were consistently classified as acute inflammations. So were all patients with abscesses in the wall of the gallbladder, even if the mucosa had healed and the wall become fibrous. Pure cases of acute cholecystitis are rather rare, i.e. first attacks in a previously healthy gallbladder. Most patients have had one or more earlier attacks which have scarred

the gallbladder or caused it to adhere to adjacent organs. It should be noted, moreover, that the inflammation was not always confined only to the gallbladder, but that there were neighbouring signs of inflammation, particularly in the hepatoduodenal ligament. In 13 per cent of the cases the acute cholecystitis was complicated with calculus in the bile ducts, with or without jaundice, and in 6.8 per cent with pancreatitis.

Chronic cholecystitis may either be the result of a slowly progressing infection or of residual lesions after acute cholecystitis that has healed previously. Also chronic cholecystitis may be combined with chronic inflammation in the bile ducts, with or without concrements. Twenty per cent of the cases of chronic cholecystitis also had calculus in the choledochus, and 13 per cent were complicated with pancreatitis.

In the cases of cholelithiasis, 22.7 per cent had calculus in the bile ducts and 23 per cent were complicated with pancreatitis.

The subjoined table I shows the distribution of the patients according to age and sex. The women are in five-fold majority as compared to the men. Most of the persons belong to the age group 50—59 years. The total mortality was 6.5 per cent, 5 per cent for women and 14.2 per cent for men. Below 55 years the mortality was only 2.4 per cent.

Table I.

	Less than 20 years	20–29	30–39	40–49	50–59	60–69	More than 70 years	Total
Men	1	4	6	11	15	19	3	59
Women	—	29	54	77	86	56	9	311

b. Excision of Samples.

The liver specimens on which the present investigation is based were taken in the course of operations from the edge of the liver. Since in the majority of cases most of the edge was very sharp, owing to regressive changes with atrophy of the liver parenchyma and relative proliferation of connective tissue and its vessels and bile ducts (Aiello), the sample was excised from a rounded portion of the edge that had the same macroscopic appearance as the liver elsewhere. A suitable place could always be found in the left lobe, some cm to the left of the falciform ligament. This position has the additional advantage that it is at a safe distance from the gallbladder; consequently any inflammatory process in the wall of the gallbladder could not by direct transference have affected the liver at the site of the sample. The excised sample was usually about the size of a finger nail and penetrated about 1 cm of the parenchyma. In a few cases, a sample was excised and a piece

extracted from the bottom of the wound by puncture biopsy. In 67 instances, 2 samples were excised from the same liver, one from the left and one from the right lobe, the sample from the right love being taken 5—8 cm to the right of the gallbladder.

The samples were excised at the beginning of the operation, usually while waiting for the cholangiogram to be developed. The samples from the liver were immediately divided into 2 pieces which at once were immersed into their respective storage fluids: alcohol for glycogen staining and formalin for cell, connective tissue and fat staining. In no case was the excision of a sample from the liver attended by any complications. The insignificant hemorrhage associated with the excision stopped immediately when the liver was sutured. The sample was always removed with a knife in order to avoid formation of such artefactive products as may be caused by using diathermy.

c. Normals.

Owing to its detoxifying function, the liver will be subjected to a number of harmful effects which very early in life can be traced in the histologic structure. Consequently it is difficult to find a series of normals, and it is therefore necessary to remain content with a normal material consisting of liver sections from clinically healthy persons who have been operated on for a disorder without influence on the liver. Thus, as appears in table II, my normal series includes cases of traumatic abdominal damage, foreign bodies in the intestinal tract which have not lesioned the mucosa and other cases without signs of bacterial infection. The liver from such patients will only exhibit traces of the lesions normally caused by the detoxifying function of the organ.

Table II. *Normal subjects.*

Diary No	Age and sex	Diagnosis	Simult. Disease	Prev. Disease	Liver (micr.)			
					Fat	Glycog.	Lympho. inf.	Hepatitis
B 1477/48*	6/12 f	Corp. alien. ventric.	—	—	—	+++	—	—
U 1683/47	5 f	Ruptur. hep.	—	—	—	+++	—	—
S 1251/45	54 m	Myalgia ep.	—	ulc. duod.	—	++	—	—
S 1442/45	40 f	Myalgia ep.	—	app. chr.	+	+++	+	—
S 4337/45	36 m	Ruptur. hep.	—	—	—	++	—	—
U 3919/49	49 f	Haematom. pariet. abd.	—	—	—	+++	—	—
B 1580/48*	52 m	Susp. ca ventr.	—	—	+	+++	—	—

* Cases from Bollnäs hospital.

d. Controls.

In order to facilitate interpretation of the changes in the liver associated with an attack of acute cholelithiasis, as distinguished from those caused by the gallstone disease as such, I have selected a control series of patients with gallstone disease in the latent stage, i.e. before an attack of cholelithiasis has been experienced or later than 36 days after the last attack. Since the investigation into the nature of acute cholecystogenic hepatitis has shown that the disease only exceptionally occurs later than about 3 weeks after an attack, the cases could have been included in the control series in which the sample was excised 22—36 days after the attack, provided that such cases had been excluded in which the acute irritability of the walls of the bile ducts remained. The control cases are entered in the table on p. 227 with spaced bold.

*

Since the normals and controls were selected in the above manner, no lesions suggestive of the type of acute hepatitis to be described in the following could be demonstrated among them.

CHAPTER III.

The Microscopical Structure of the Liver and the Circulation in the Liver.

The liver is built up from lobules of the approximate size of pin-heads. According to the opinion commonly represented in textbooks, the lobules are composed of polyhedral cells arranged in radiating cords, forming a fine network. The stroma of the liver is composed of connective tissue cords coming from its connective tissue capsules and extending between the lobules. The stroma of the liver is also known by the name Glisson's capsule. Inside the lobules the stroma is composed of a mesh of precollagenous fibres. In recent years Elias has demonstrated that these "cellular cords" are broad plates (laminae hepatis) composed of a single layer of liver cells. The cellular plates form the walls in a system of intercommunicating spaces (lacunae hepatis) that make up the hepatic labyrinth. The spaces in adjacent lobules are also intercommunicating, except where the lobules are separated by Glisson's capsule. The sinusoids in the hepatic labyrinth are suspended in the same way as the membranous labyrinth in the bony labyrinth. The lobules are separated from the connective tissue cords by a single layer of hepatic cells, lamina limitans, which has only small perforations where branches of the portal vein, hepatic artery and small bile ducts enter

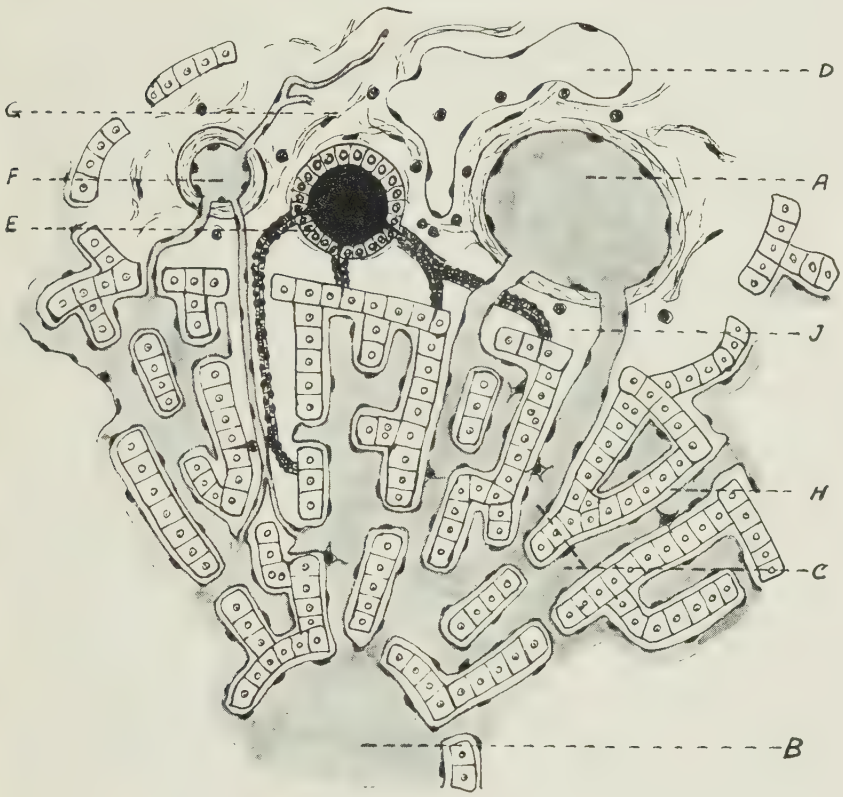

Fig. 1. Schematic diagram of a liver lobule sector.

A. Portal vein	F. Hepatic artery
B. Central vein	G. Glisson's capsule
C. Sinusoids	H. Perivascular space
D. Lymph vessel	I. Perilobular lymph space
E. Bile duct	

the lobules, when they have left Glisson's capsule. Depressions in the hepatic cells form an intercellular network of biliary capillaries emptying both into small biliary intralobular canals and via the lamina limitans into small bile ducts in Glisson's capsule. Branches of the portal vein enter the intralobular spaces in which they form a network of wide capillaries, sinusoids, which empty centrally into vena centralis, the finest branch of the hepatic vein. Apart from endothelial cells the walls of the sinusoids are composed of Kuppfer cells belonging to the reticuloendothelial system. In addition to the distribution to Glisson's capsule, the hepatic artery has very long, rectilinear, arterial capillaries

entering the lobules. These capillaries totally lack the tunica media. Such first order capillaries send out branches of second-order capillaries. These hepatic arteries supply the central portions of the lobules (Cronszscewsky 1866, Elias 1949). The arterial capillaries open into the central sinusoids and are provided with an endothelial sphincter (Elias). There are also arterial capillaries emptying into the peripheral sinusoids. Such capillaries are often surrounded by small ganglia or chromaffin cells.

The interlobular connective tissue contains endotheliumclad lymphatics that do not enter the lobules. Between the hepatocellular plates and the sinusoids there are spaces, perivascular spaces (Disse's spaces), which via the perforations in the lamina limitans communicate with extralobular spaces between the lamina limitans and the interlobular connective tissue, so called perilobular lymph spaces (Mall 1906). From these spaces the lymph is capable of entering the lymphatics in Glisson's capsule. The connective tissue of the portal cords in addition to the portal vein contains the hepatic artery, lymphatics and bile ducts as well as localized aggregations of histocytes and lymphocytes (Virschow's lymphoma). Their presence has attracted much attention and often been held as a sign of interstitial hepatitis. They may undoubtedly be considered to have some connection with inflammatory processes in the liver. However, the most varying reasons have been found for their occurrence, e.g. various toxic infections in different organs (Rössle, Lubarsch, Siegmund, Sysaek, Kahldorf, Sternberg, Wagner, Kettler, Fraenkel, etc. cited from La Manna). Enlargement of the infiltrates probably has to do with the considerable detoxifying capacity of the liver on its blood supply. The focus of the infection that has caused this development need therefore not be located in the liver or its extrabiliary system, nor even in the distributive area of the portal vein. The genesis of these infiltrates depends on the kind and strength of the poison as well as on the period of action of the toxin in the various diseases. The localization around the bile ducts has often given rise to the diagnosis: pericholangitic foci, and for this reason it has not been far-fetched to interpret them as suggestive of cholangitis. This conclusion is not justified from pathoanatomic points of view, for cholangitis implies an inflammatory process that affects also the bile duct itself with epithelial lesions and invasion of leukocytes through the wall. Instead, pathologists consider these infiltrates in the portal cords as an indication of the toxin absorption of the liver, which toxins it gets rid of via the lymphatics (Rössle).

In my view it seems as though lymphocyte infiltrates were the predominant feature of the hepatitic picture on which are based most of the clinical works on liver changes associated with cholecystitis. It may therefore be suitable to describe my observations concerning such infiltrations in my series, although they cannot be said to belong to the

form of acute cholecystogenic hepatitis to be dealt with in the following. First of all it should be noted that the lymphocyte infiltrations occur in all the age groups represented by my series. They occur not only in inflammatory conditions in the bile ducts but also in uncomplicated cholelithiases (cf. p. 209). They are most frequent in acute cholecystitis (55 per cent), less so in chronic cholecystitis (31 per cent), and in cholelithiasis they only amount to 23 per cent. Since with increasing age patients have passed through more diseases and the gallstone affection has developed further and given rise to more complications with infection, the infiltrates in persons of a more mature age should have a somewhat higher frequency. This is the case of my series, but the increas in area of the lymphocyte infiltrates is negligible with advancing age.

A study of the lymphocyte infiltrates in my series indicated that they increased not only because of the normal detoxifying function of the liver, but also owing to such factors as concomitant inflammatory processes in the bile ducts.

The demonstrated increase of the infiltrates in acute cholecystitis is partly due to a change in the composition of the infiltrates when the gallbladder is affected by acute inflammatory processes. Then, in addition to the usual types of cells, there is a greater or lesser admixture of leukocytes. This admixture always commences in the periphery of the lobules, particularly around the bile canaliculi (fig. 18), and later spreads out in the periportal tissue. The leukocytes appear very soon after an attack of cholelithiasis (during the next few days) and seem to vanish as the acute cholecystitis recedes. Similar accumulations of leukocytes have been observed also in general infections with staphylococci and streptococci ("Bahrmann's Ausscheidungscholangitis"). In rare cases such an admixture with leukocytes may become so large that the infiltrates take on the appearance of multiple abscesses. Then, the lesions may develop into real cholangitis with damage to the small bile ducts and leukocyte invasion into their lumens (fig. 19). The large bile ducts, on the other hand, appear to remain intact and only very occasionally do their lumens contain any pus cells without exhibiting any wall changes. In a manner of speaking, therefore, the liver drains itself to the intestine via the bile ducts. I consequently find it probable that in rare cases (3 in my series) the detoxifying function of the liver may induce purulent inflammations in the portal cords with gradual involvement of the bile ducts. Since inflammation in the portal connective tissue only is much commoner than in both portal connective tissue and the bile ducts, and since I never have seen any example of inflammation confined only to the bile ducts, I am inclined to think it unlikely that the infection in the portal cords usually is ascending. Whether in cases when there are clinical signs of cholangitis, the inflammation is confined to the large bile ducts, as is held by LAMANNA, cannot be said on the basis of my slides.

It may be suitable to make some additional statements concerning the circulation in the liver. Blood from the greater part of the abdominal viscera drains into the portal vein, which in the hilus of the liver divides into two large branches, one to the right and one to the left lobe of the liver. The drainage areas of the two branches adjoin so that the marginal line passes through the bed of the gallbladder and not along the anatomical border in level with the falciform ligament. While coursing through the main stem of the portal vein the blood drained from the right half of the abdomen does not usually mix to any significant extent with that coming from the left half; consequently most of the blood from the right half of the abdomen goes to the right lobe of the liver and the blood from the left half of the abdomen (including the spleen) to the left lobe. The portal vein subdivides into increasingly smaller branches which finally reach the periphery of the lobules and joins the sinusoids. The latter run centripetally towards the centre of the lobules where they join, forming the central vein. The hepatic artery is located alongside the portal vein and has tributaries to Glisson's capsule and its structures. These capillaries are either directly or via small veins interconnected with the intralobular capillaries. Even the central sinusoids are supplied by arterial capillaries. It is assumed that the hepatic cells thereby obtain blood rich in oxygen. It is also presumed, however, that oxygen is set free in the course of the intermediary metabilic process carried on in the liver, and that this oxygen goes to the cells and that anaerobic metabolism can take place centrally in the lobules. Nevertheless, the hepatic artery is essential to the life of the liver cells, and if this artery is tied off fatal necrosis will result. Thrombosis of the portal vein does not as a rule lead to infarction in the liver, provided that the hepatic artery can maintain an adequate collateral supply of blood.

The wall of the intralobular capillaries of the liver is thin. The lumen is wide, in places curviform (sinusoid). In the syncytial tube of endothelium the nuclei are spaced far apart and it is invested by a network of fibres. The capillary wall abuts on the hepatic cells or is separated from them by a perivascular space whose tissue fluid drains outwards to the portal cords where it reaches the lymphatics. It is generally held that the intralobular capillaries do not contract spontaneously but that their width is regulated by hepatocellular congestion. The capillary wall also contains so called Kupffer cells which are spread throughout the capillary and belong to the reticuloendothelial system. These cells are phagocytic and engorge foreign bodies, e.g. cellular fragments and bacteria from the portal blood, but they can also assimilate dead red blood corpuscles and form biliary colouring matter (bilirubin) from the products of decomposition. It is uncertain whether Kupffer cells are also capable of transferring substances from the blood to the hepatic cells. According to old observations, that have been further confirmed by Fleischl, Kunkel, Kufferath, and Harley (cited from Kodama),

it has been found that a ligation of the choledochus causes a passage of bile over into the lymphatics and in case the thoracic duct is also ligated no bile or only a trace of bile ever reaches the blood. Also after injection of dyestuff into the bile ducts, the dye leaves the ducts in the periphery of the lobules and enters the perivascular lymph spaces surrounding the blood capillaries. These spaces communicate at the periphery of the lobules with the perilobular lymph spaces which reach the lymphatics in Glisson's capsule. As appears in the review of literature much attention has been given in discussions on the relationship between cholecystitis and hepatitis to the lymph circulation in the liver and especially that between the latter and the gallbladder.

Ever since STARLING reported that ligation of the inferior vena cava above the opening of the hepatic vein causes a marked increase in the flow of lymph from the thoracic duct, it has been held that the liver is the producer of most of the lymph in the thoracic duct. MARKOWITZ & MANN (1930), on the other hand, found in hepatectomized dogs that the lymph flow decreased little if at all after removal of the liver. The animals responded to lymphagogues as before with much increased flow of lymph in the thoracic duct.

Few attempts have been made to study unmixed lymph from the liver, most authors having drawn the lymph from the thoracic duct on the neck and indirectly determined the flow of lymph from the liver. CAIN, GRINDLAY, BOLLMAN, FLOCK, & MANN (1941) have made interesting experiments on dogs, involving drainage of lymph from the liver in the hepatoduodenal ligament and from the thoracic duct on the neck. They found that the mean lymph flow from the intrahepatic lymphatics was 2.6 cc per 10 min. and 4.6 cc per 10 min. from the thoracic duct and maintain that the liver probably produces 1/4—1/2 of the total lymph in the thoracic duct. Acute carbon tetrachloride intoxication did not markedly change the lymph from the liver except that it was mixed with blood. The protein content of the hepatic lymph was approximately 5 6th of that in blood plasma and in the lymph of the thoracic duct approximately 1 2 that of plasma. With respect to chlorides and phosphates, the salt content was the same as that in the blood.

Thus, an appreciable amount of protein-rich lymph is formed in the liver and the flow of lymph from the organ, which mainly runs to porta hepatis, must therefore be considerable. The gallbladder, which has not the same profuse blood supply as the liver, must have a relatively smaller production of lymph. Injection experiments with dyes reveal that the lymph from the gallbladder flows along the cystic duct down to lymphoglandulae cysticae and further to lymphoglandulae coeliacae. When the injection is performed into the wall of the gallbladder some dye also passes over to the liver. It does not seem likely, however, that the gallbladder lymph should enter and infect the whole liver; at most it can infect the bed of the gallbladder. In the present investigation

I have sometimes also studied a piece of the liver from the bed of the gallbladder, but I have not observed hepatitis in a greater frequency. Instead, I have found that hepatitis can be demonstrated in both lobes of the liver without being present in the bed of the gallbladder which, on the other hand, often contains large infiltrates of lymphocytes in the portal cords. According to injection experiments, lymph from the abdominal organs does not pass to the liver.

How does this fit in with the investigations made by HARER, HAGIS, & VAN METER? (cf. p. 185). The answer is that the absorption from the gallbladder chiefly takes place via the veins (PETRÉN) and it is therefore probable that also a salt of rhodanic acid introduced into the gallbladder is also absorbed by the same route. In the lobules of the liver, on the other hand, it can be separated with the lymph, in which it can be demonstrated, although it need not have come directly via the lymphatics.

CHAPTER IV.

The Patho-anatomic Picture of Cholecystogenic Acute Hepatitis.

In Chapter I, p. 180, there is a review of earlier findings concerning liver changes in connection with cholecystitis, and it appears that almost all investigators have observed hepatitic changes. It also appears, however, that all sorts of inflammatory reactions in the liver have been used in support of the diagnosis "hepatitis." The rule has been to accord much weight to the infiltrates of lymphocytes that so often are present in the portal cords and that are discussed on p. 196. However, hepatitis in the strict sense of the term implies parenchymal damage. Such damage in cholelithiasis has been described very inadequately, e.g. as "cellular degeneration," "slight necrosis," etc., but most often no parenchymal damage has been observed. As my cases have increased in number, it has become ever clearer that cholecystitis is associated with a form of acute hepatitis which is definitive and has a fully characteristic picture.

In my series of gallbladder affections, I have observed in the excised liver samples from 104 of 370 of the patients the changes characteristic of the form of acute hepatitis mentioned above. As a rule the lesions were fairly mild and never so extensive as in virus hepatitis (figs. 13, 14).

The surface of the liver exhibits no macroscopically visible characteristics of cholecystogenic acute hepatitis. As emphasized in chapter I, it has been known for a long time that the liver is swollen in association with cholecystitis. It is very possible that this swelling is caused by the acute hepatitis. It was observed in practically all

cases when the liver sample showed signs of hepatitis, but also sometimes when there was no hepatitis. Swelling of the liver is manifested as enlargement of the organ, whose edges become rounded. Moreover, the surface of the liver becomes irregular because parts rich in parenchyma rise above those rich in connective tissue. The irregularity is most marked along the edge of the right lobe. Swelling of Riedel's lobe is another sign of the same phenomenon; the lobe may often be seen curving its way between the shrunken gallbladder and the falciform ligament.

As pointed out elsewhere, however, the comparatively small liver sample cannot always be representative of the whole organ; consequently the presence and least of all the absence of hepatitis in the slide under inspection should not provide grounds for too far-reaching conclusions. Since hepatocellular necrosis cannot be observed in the controls, the presence of even a minute number of necrotized cells must be enough to confirm a diagnosis of hepatitis.

Concerning the appearance of the type of hepatitis occurring in connection with gallbladder affections, it may be said that there is nothing remarkable about its patho-anatomic picture. The first sign visible in the slide is necrosis of the liver cells whose protoplasm becomes compact and acidophilic and whose nuclei pycnotic (fig. 22). The tissue is invaded by polynucleated white blood corpuscles, the number of which increases as the cells disintegrate into smaller cellular fragments. Therefore, within the lesioned parts of the liver there are seen accumulations of white blood corpuscles among hepatocellular remains or around a necrotic but not yet disintegrated cell (figs. 20, 21). The picture is rather similar to that seen in toxic hepatitis, as it is manifested after carbon tetrachloride intoxication or the like. In more advanced stages, also solitary mononucleated cells may be seen in the infiltrates, but no tissue reaction with connective tissue regeneration is visible. On the other hand, the hepatized area sometimes contains oval or irregularly shaped cells whose protoplasm contains an abundance of yellow-brown pigment granules. They have the same appearance as the pigmented cells that are seen in virus hepatitis and that are thought to be histocytes which have absorbed lipofuscin from disintegrating liver cells. "Lipofuscin is probably a normal pigment of the liver cells which is liberated and rapidly phagocytized when these cells disintegrate. It thus serves as an indicator of breakdown of hepatic parenchyma. The pigmented macrophages may persist for long periods." (Lucké). The leukocytes finally disappear from the old foci of disintegration and only some lymphocytes among pigmented cells and some proliferated biliary ducts are visible.

The destructive changes usually, if not always, begin in the central part of the lobule, for in the earliest cases of the series only the central zones of the lobule are involved. Even in more protracted cases, many

lobules are encountered in which the damage is limited to the central regions, leaving intact the peripheral parts of the liver tissue. The lesions do not involve all the lobules to the same degree; they range from destruction of a few liver cells in the central zones to about 20 per cent of the parenchymal cells of the lobule.

The hepatitic changes described above were more or less extensive in my series. I have therefore graded the extent of the changes in the slides from + to + + +. Sign + denotes that the parenchymal damage only involved solitary cells in the lobules, from 1 4 necrotic liver cells being seen in a field of vision including about 100 cells (400 diameters magnification); + + implies the presence of 5—10 destroyed cells in a field of vision of the same size under the same magnification; + + + refers to the most extensive damage seen in cholecystogenic acute hepatitis, with degenerative foci comprising more than 10 cells and often involving considerable numbers of the parenchymal cells in the lobule. In the first group, as a rule, only some of the lobules contain degenerated cells. The degree of hepatitis was usually not higher than that classed as + (66 per cent), whereas the most extensive damage occurred in only about 5 per cent of my series. Owing to the focal character of the lesions, those seen in the slide need not be representative of the entire liver. Even if the excised piece is undamaged, lesions may be present in the rest of the organ. In the 67 instances when I excised two samples from the liver, one from the right and one from the left lobe, changes suggestive of hepatitis occurred in practically the same frequencies in both lobes. This appears from table III.

Table III. *The degree of hepatitis in the samples from both liver lobes.*

Combination	No. of patients	Combination	No. of patients
L— R—	37	L+++ R—	0
L+ R+	6	L— R+++	0
L++ R++	2	L++ R+	3
L+++ R+++	1	L+ R++	3
L+ R—	4	L+++ R+	1
L— R+	5	L+ R+++	0
L++ R—	2	L+++ R++	0
L— R++	2	L++ R+++	0

Equal in 46 cases; L-dominance in 10 cases; R-dominance in 11 cases.

The series on which I have based my study comprises 370 average cases of gallstone disease. The cases were assembled without being selected from two large surgical clinics. The distribution of the patients into the different classes of gallstone disease will be seen in table IV,

which also gives the number of cases of acute hepatitis as well as the distribution of the different degrees of hepatitis in each class.

Table IV.

Disease group	No. of cases	No. of hepatit.	Per cent hepatit.	Degree of hepatitis		
				+	++	+++
Cholecystitis ac.	177	49	28.7	71 %	25 %	4 %
Cholecystitis chr.	108	33	30.6	58 %	33 %	9 %
Cholelithiasis	85	22	25.9	68 %	32 %	0 %
Total	370	104	28.1	66 %	29 %	5 %

It will be seen that the cases of acute hepatitis are fairly evenly distributed in the various disease groups.

In addition to the above observations concerning the histological picture of cholecystogenic acute hepatitis, I have by special staining methods investigated the hepatocellular content of glycogen and fat. The content was estimated by assaying the stainability for glycogen and fat, respectively, and the graded colourations were classified under the groups O and + to +++. O signifies no stained substance, + traces, ++ moderate and +++ plenty of stained matter. This classification was subjective, of course, but by repeated estimations of the glycogen and fat content, respectively, in the different slides, it turned out that there was no essential difference between the several estimations. In experimentally induced toxic hepatitis, the first observed sign of intoxication has been resolution of the cellular glycogen and the second fatty infiltration in the cells. In order to study these matters in my series of patients, I have tabulated the respective glycogen and fat contents in the separate cases and then computed the mean glycogen and fat contents on different days after the attack of gallstone disease. In so doing, I applied the classification into 3 day groups for the frequency of hepatitis on different days after the acute attack of cholelithiasis. The result of these computations appears from fig. 2.

The computations reveal that the hepatic glycogen content is considerably reduced during the first 6 days after the attack, but that from then on it gradually increases and reaches a constant level after 3 weeks. The corresponding curve for the fat content in the liver is not of the same characteristic shape (fig. 3). It exhibits only small variations, possibly with slightly higher values during the first days after the attack.

As my series of cases was assembled at two different hospitals with slightly dissimilar indications for operation and since different living conditions in the two districts may influence the factors giving rise to hepatitis, I have found it appropriate to divide the series into two groups. One group is composed of patients from the hospital at Sundsvall (group

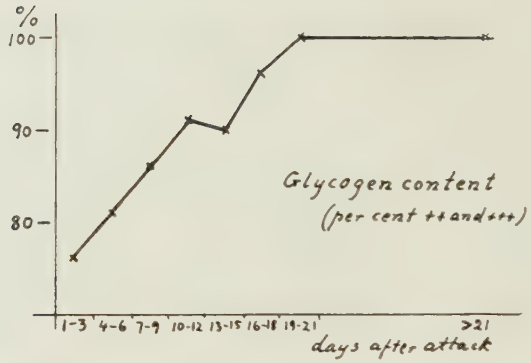

Fig. 2. Average glycogen content of the liver on different days after the attack of gallstone disease.

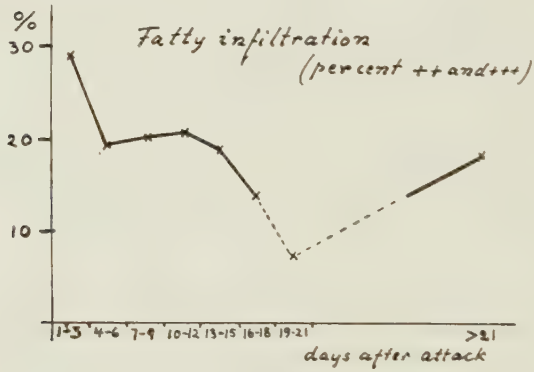

Fig. 3. Average fatty infiltration of the liver on different days after the attack of gallstone disease.

S), and the patients in the other group came from the University Hospital Uppsala (group U). The patients in group S came from a district in northern Sweden where the staple industries are forestry and wood-pulp working. The "group U" persons came from an agricultural and industrial region in central Sweden. The living standard of group S is perhaps somewhat lower than that of group U, even under normal conditions. Owing to the hardships imposed by the war, however, the living standard of group S during the period when the series was assembled was even further reduced below that of group U. It is interesting to note, therefore, that the frequency of hepatitis in the two groups was markedly dissimilar.

Table V. *The Frequency of Hepatitis in the two groupes U and S for the period 1—36 days after the attack of gallstone disease.*

Group U ..... 67/145 = 46.2 ± 4.1 per cent
Group S ..... 37/225 = 16.4 ± 2.4 per cent.

Difference between the groups is 29.8 ± 4.8 per cent.

CHAPTER V.

The Relation of Hepatitis to different Factors in the Acute Attack of Gallstone Disease.

a. Hepatitis and General Factors.

Table VI. *Frequency of hepatitis according to age and sex.*

Sex	< 30 years	30—39	40—49	50—59	60—69	≥ 70 years	Total
♀	6/29=21 %	13/54=24 %	23/77=31 %	30/86=35 %	14/56=25 %	2/9 =22 %	88/311=28 %
♂	2/5 =40 %	1/6 =17%	3/11=27 %	3/15=20 %	6/19=32 %	1/3 =33 %	16/59 =27 %
♀+♂	8/34=23 %	14/60=23 %	26/88=30 %	33/101=33 %	20/75=27 %	3/12=25 %	104/370=28 %

Table VII. *The frequency of hepatitis in the months of the year*

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
S.	3/9	1/13	4/22	3/25	8/30	5/25	6/25	1/13	3/17	0/15	3/19	0/12
U.	7/14	6/13	10/20	2/12	1/6	3/5	2/3	5/14	3/6	8/13	12/24	8/15

	S.	U.
Frequency during the summer season:	19.3 ± 3.4 %	32.6 ± 6.9 %
,, ,, ,, winter ,,	12.2 ± 3.4 %	52.5 ± 5 %
Difference:	—7.1 ± 4.8 %	19.9 ± 8.5 %

It is remarkable that the difference between the summer and winter frequencies of hepatitis is manifest only in the U-series, with its higher average frequency.

In table VI, the cases of hepatitis have been classified according to sex and age of the patient. The frequency of hepatitis in women was 28 per cent (88 of 311) and in men 27 per cent (16 of 59). Thus, there was no sex-linked difference. It should be noted, moreover, that there is no significant difference between the various age groups.

Since, according to an old observation, pregnancy promotes the onset of cholelithiasis, it might be of interest to investigate whether

pregnancy also affect the susceptibility to hepatitis of the liver. Such a comparison shows that the frequency of hepatitis among nulliparae in my series is 6/15 which corresponds to 40 ± 12.6 per cent. The frequency of hepatitis among women with one or more previous parturitions is 40/191 or 26.4 ± 3.6 per cent. The difference is 13.6 ± 13.1 per cent, and is therefore not statistical.

b. The Relation in Time of Hepatitis to the Attack of Gallstone Disease.

The diagrams in figs. 4, 5 and 6 show the frequency of hepatitis after a varying number of attacks. After the first attack, the frequency in the two groups was 11.1 and 27.3 per cent, respectively. The corresponding figures after two or more attacks of gallstone disease was 18.5 and 49.6 per cent. In the two groups together the differens is significant 31.9 ± 2.8 % — 15.3 ± 3.9 % = 16.6 ± 4.8 %.

Starting from the most recent attack of gallstone disease and arranging the patients according to the time elapsed before the sample was excised, we shall obtain the distribution illustrated by diagrams in figs. 7, 8 and 9. Apart from the dissimilar frequencies in the two groups, the agreement between the curves is quite good. During the first 3 days, the frequency of hepatitis was moderate. During the next 14 days the frequency was high and stable; thereafter it dropped and was low after 3 weeks. This curve might indicate that cholecystogenic hepatitis develops for 3 days, is at a maximum for the next 14 days, and thereafter gradually disappears. It is likewise possible, however, that each onset of hepatitis is rather brief but that the sum of several onsets constitutes a fairly protracted diseased condition which lasts as long as the factor causing hepatitis is effective. A third possibility is that hepatitis in the individual case sets in at varying intervals after the acute attack of cholelithiasis, which would make the curve for the sum of the cases of hepatitis more elongated than that representing an individual case of the disorder.

It was found that, in the cases when hepatitis was present more than 3 weeks later than the attack of acute gallstone disease, after 22 days (144) signs were still present of acute inflammation of the biliary ducts, with pus in the choledochus and suppurative inflammation in the gallbladder mucosa. The patient (314) whose hepatitis was present 24 days after the acute attack suffered from a manic-depressive psychosis and was preoperatively given electric shock treatment, the true interval therefore being uncertain. In the third case (298), 36 days after the attack of gallstone disease, the patient still had pus in the gallbladder, the mucosa of which was ulcerated. (Bacterial culture: alphahemolytic streptococci.)

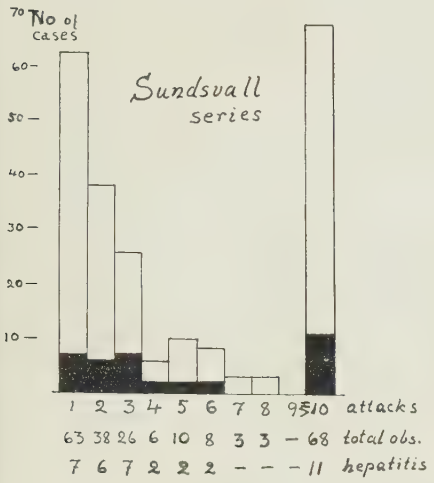

Fig. 4.

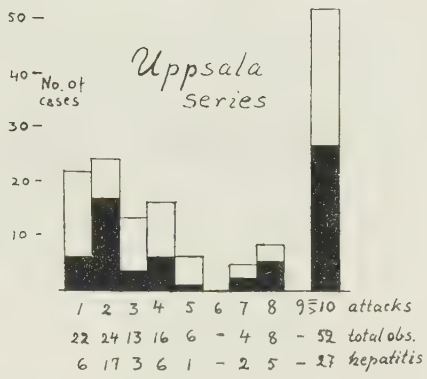

Fig. 5.

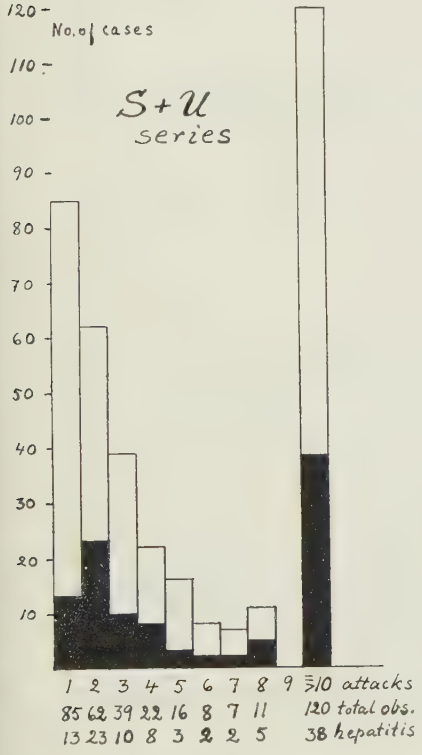

Fig. 6.

Fig. 4, 5 and 6. Frequency of hepatitis after different number of attacks of gallstone disease. Sundsvall, Uppsala and S + U series.

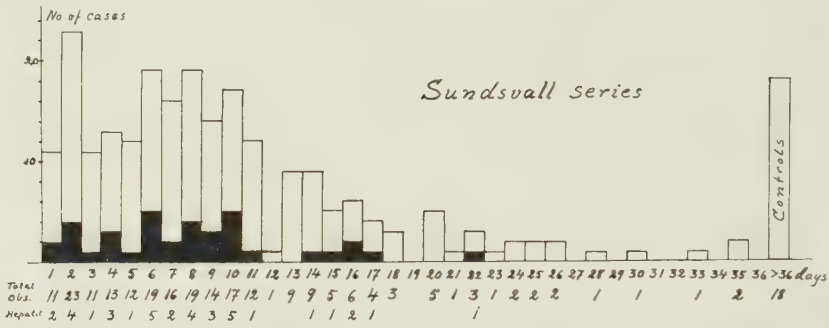

Fig. 7. Frequency of hepatitis on different days after attack of gallstone disease. (Sundsvall series.)

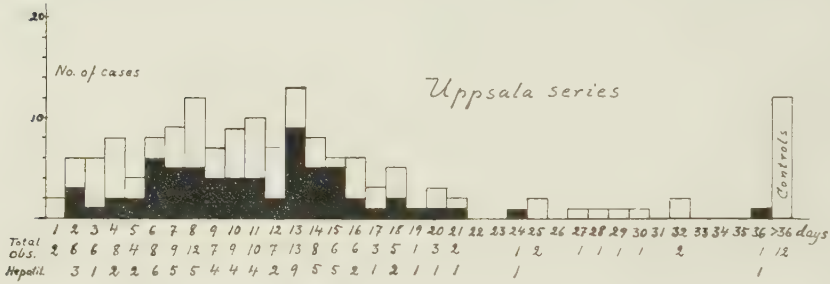

Fig. 8. Frequency of hepatitis on different days after attack of gallstone disease. (Uppsala series.)

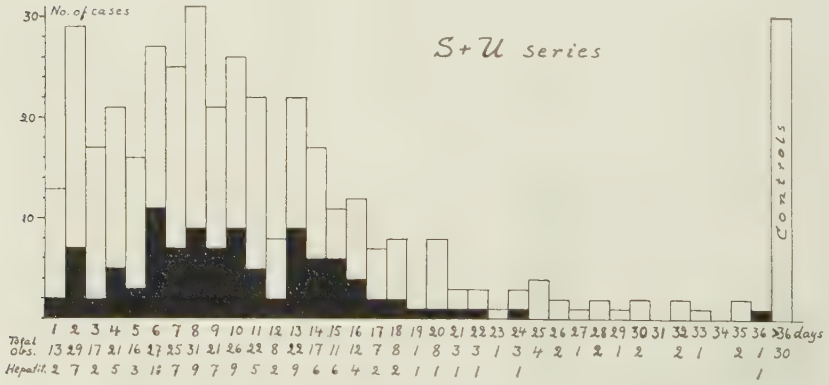

Fig. 9. Frequency of hepatitis on different days after attack of gallstone disease. (Sundsvall + Uppsala series.)

c. Hepatitis and Gallbladder Changes.

1. Changes in the contents.

Most of the patients in the series had one or more calculi in the gallbladder. In the small number of cases without calculus in the gallbladder, the latter was characterized by marked anatomic and functional changes of an inflammatory nature. All told there were 9 such cases, viz. 2 of acute cholecystitis (55 and 97), 5 of chronic cholecystitis (52, 139, 155, 370 and 378), and 2 of cholesterosis of the gallbladder (365 and 399). In some cases the gallbladder at operation to be sure contained no calculus, but then the choledochus instead held typical gallbladder calculi, or there was distention of the cystic duct and choledochus which indicated passage of calculi from the gallbladder. (The latter cases were nos. 377, 372 and 327.)

In some cases the gallbladder contents was examined microscopically to see if it contained pus cells and bacteria, in others bacterial cultures were made. Microscopical examination was as a rule performed in all cases when the macroscopic appearance of the contents was suggestive of infection. The results of these examinations are entered in table VIII.

Table VIII. *Changes in the gallbladder contents.*

Cases with hepatitis	neg.	a few leukoc., nil bacteria	Pus, nil bacter.	Pus & bacter.
47	4 (9 %)	23 (49 %)	6 (12 %)	14 (30 %)
Without hepatitis				
112	14 (12.5)	49 (44 %)	14 (12.5 %)	35 (31 %)

The table reveals that the risk of infection in the contents of the gallbladder in the patients with hepatitis was practically the same as in the patients without hepatitis. The factors studied in the gallbladder contents thus provide no explanation why hepatitis sometimes sets in after gallbladder affections. The existence of biliary calculi in the gallbladder has not been discussed separately because, as mentioned above, practically all the patients had biliary calculi. However, as appears in the chapter on the development of cholecystitis, the significance attributed to concrements lodged in the neck of the gallbladder should always be kept in mind.

2. Changes in the wall.

In table IV, p. 203, a review was given of the frequency of hepatitis in the different groups of gallbladder changes, and it turned out that,

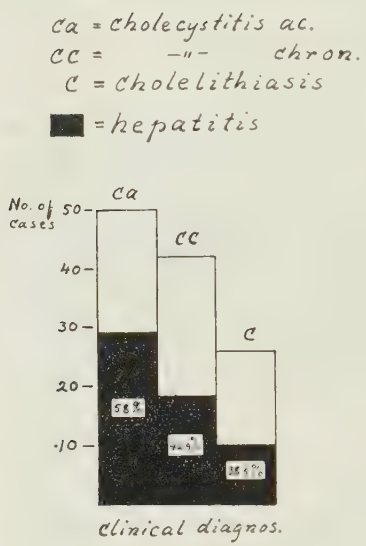

Fig. 10.

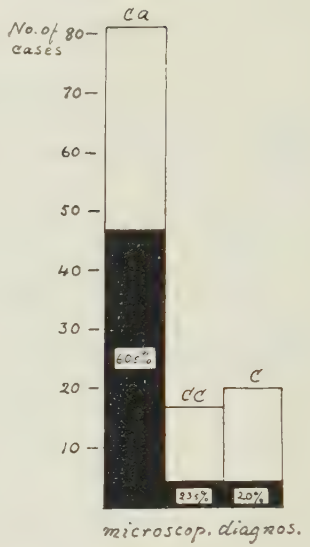

Fig. 11.

Fig. 10 and 11. Frequency of hepatitis by gallstone diseases classified according to clinical (macroscopic) and microscopic diagnosis. (126 cases from Uppsala series.) According to macroscopical diagnosis the difference between ca, on the one hand, and cc and c, on the other hand, is $58.0 \pm 7.0 - 41.2 \pm 6.0$ per cent $= 16.8 \pm 9.2$ per cent, which is neither probable nor significant. Microscopically, however, the same difference is $60.5 \pm 5.4 - 21.6 \pm 6.7$ per cent $= 38.9 \pm 8.7$ per cent and significant.

when the gallbladder changes were classified according to clinical signs, inflammatory changes were followed by a negligibly higher frequency of hepatitis, viz. 28.7 per cent in acute and 30.6 per cent in chronic cholecystitis and 25.9 per cent in cholelithiasis without macroscopical signs of inflammation. Furthermore, it appeared that the most grave lesions in the liver occurred only in association with inflammatory processes in the gallbladder.

If the gallbladder changes are classified according to their histopathologic appearance instead of clinically, the position will be quite different. In order to check up on the reliability of the clinical diagnoses of the gallbladder affections included in my series, I have in a certain number of cases examined the gallbladder microscopically. For this purpose I saved a 1.5 cm long strip from the central zone of the gallbladder, which macroscopically represented the average appearance of the organ. Microscopic slides from 126 gallbladders were thus examined, and hepatitis was present in the liver of 57 of these patients.

A clinical grouping of these gallbladders is illustrated in fig. 10 where the blacked-in part of the columns represents the frequency of hepa-

titis among the patients. The same gallbladders were then grouped according to the microscopical diagnoses, and the distribution into various disease groups will be seen in fig. 11. It should be noted that the group with acute cholecystitis now is considerably greater, whereas the other groups are correspondingly smaller. This is particularly true of chronic cholecystitis in which the acute feature is difficult to observe macroscopically. However, also the group with cholelithiasis has lost some patients to the group with acute inflammation. In these cases microscopical examination of the gallbladder reveals distinct signs of acute inflammation, although many of the patients lacked macroscopical signs of such changes. Most often the microscopical sign was more or less marked infiltration of leukocytes in the gallbladder mucosa (fig. 15) or the tissue of the wall. At other times the tissues were distinctly edematous. In some cases, the sole sign of acute inflammation was progressive migration of leukocytes from the small veins in the mucosa and, predominantly, the deep layers of the wall (fig. 16), especially the serous membrane. Here the veins were often congested with leukocytes which in large numbers also had invaded the venous wall as well as the surrounding tissues (fig. 17). None of these phenomena are at all macroscopically visible, and unless the gallbladder is affected by other inflammatory processes as well, the cases concerned will clinically be classed as non-inflamed. Such inflammatory processes in the venous system of the gallbladder are of particular interest when the cause of hepatitis is looked for in the region drained by the portal vein, in which as we know the gallbladder is included. Since my examination involved only a small portion of the gallbladder, it is not impossible that the patients in whom I had observed no signs of acute inflammation in the wall of the gallbladder, all the same might have had an inflammatory process in another part of the organ. As stated in the chapter on the development of cholecystitis, it is not improbable that cholecystitis in some patients commences in the deep layers of the gallbladder and at second hand attacks the mucosa so that the contents becomes infected.

The most remarkable feature of the new classification is that it predominantly is the patients with hepatitis who have moved over to the group with acute cholecystitis. Now 49 of the 57 patients with hepatitis belong in the group with acute cholecystitis, 4 in the group with chronic cholecystitis and 4 in the group with cholelithiasis. The frequency of hepatitis in the group with acute cholecystitis has therefore increased. It may also be said that hepatitis and acute cholecystitis tend to go together.

d. Hepatitis and Pancreatic Changes.

The pancreas is the abdominal organ that is in closest contact with the bile ducts and the liver. Since in activated form its juice is very

destructive to tissues, pancreatitis might be suspected to play a part in the etiology of hepatitis. If the series is grouped according to the maximum urinary diastase level in connection with the attack of gallstone disease, the frequency of hepatitis in the group with normal and pathologic diastase level will be seen in table IX.

No evidence has appeared that pancreatic affections have a function in the etiology of hepatitis.

Table IX. *The frequency of hepatitis for different diastase levels.*

Wohlgemuth–U/ml urine	2–6 normal	7–8 borderline	≧ 9 pathologic
S series	31/170 (18.2 %)	3/8 (16.7 %)	2 25 (8 %)
U series	46/98 (47 %)	11/21 (52.4 %)	10 23 (43.5 %)

It appears that the frequency of hepatitis is unaffected by the diastase level.

e. Hepatitis and Choledochus Obstruction.

A factor that attracts as much attention as the inflammation in the gallbladder in discussions on the etiology of hepatitis is if bile stasis caused by choledochus obstruction can give rise to hepatitis. Such obstruction is usually due to a concrement, but other causes exist. Thus, it cannot be excluded that a duodenal diverticulum or a swollen lymph node in the hepatoduodenal ligament sometimes can render difficult the outflow of bile from the liver. In my series a calculus was encountered in the choledochus in 69 cases, and hepatitis was found in 26 of these choledochus cases. The frequency of hepatitis, which averaged 28.1 per cent in the whole series, was among the choledochus cases 37.7 per cent and among the rest of the series 25.9 per cent. The difference is 11.8 ± 5.1 per cent, but the series is not sufficiently large to permit computations of significance. Among the choledochus cases the hepatitic frequency in the S series was 10 of 36 = 27.8 per cent; in the U series 16 of 33 = 48.5 per cent. In the cases without choledochus complication the frequency of hepatitis in the S series was 27 of 189 = 14.3 per cent; in the U series 51 of 112 = 45.5 per cent.

Here it must be emphasized that the above figure for the incidence of hepatitis in persons with calculus in the choledochus only refers to the form of acute necrotic hepatitis that I have described in the foregoing and not to the regressive changes that particularly affect the central zone of the lobule which is a gradual result of prolonged biliary stasis and that may give rise to biliary cirrhosis.

Acute cholecystogenic hepatitis occurs in occlusion of the choledochus only after an acute attack. It cannot therefore be caused solely by the biliary stasis, particularly as the hepatitis heals even if the jaundice

persists. Therefore, some factor other than the biliary stasis must be the one which causes acute hepatitis. The most likely factor would then be an inflammatory process in the biliary ducts simultaneously with choledocholithiasis. The coexistence of infection and choledocholithiasis is indicated by the fever which often accompanies this gallstone complication and which very often is manifested in the form of repeated chills. The commonest opinion concerning the cause of these chills is probably the one that the stagnant bile gets infected and that they are caused as a result of an ascending infection in the biliary ducts: the chills are considered an expression of ascending cholangitis. The detailed and meticulous patho-anatomic investigations by La Manna into the appearance of cholangitis in various stages of its development showed that in the first place the large bile ducts are infected and that they mostly are the seat of inflammations, whereas the small biliary ducts remain intact.

Nor have I as a rule in my studies been able to observe any inflammatory changes in those peripheral biliary canals which are to be seen in the excised samples. Whenever signs of infection were seen in the small biliary canals (11, 180, 226), it was mostly confined to the tissues outside the biliary canals and had only in places attacked their epithelium and entered them. Thus according to the picture exhibited by the microscopic slides, the infective toxins should reach the various parts of the liver by routes other than the biliary canals.

It is by no means difficult to imagine a similar mechanism for the development of hepatitis and cholangitis, whether it is secondary to cholecystitis or is derived from some other focus of infection, e.g. the wall of the choledochus. At operations for gallstone disease, it is not seldom that an inflammation is seen around the choledochus, either in the form of acute edema or fibrosis. As pointed out earlier while on the subject of lymph circulation in gallbladder and liver, it is highly improbable that the liver can be infected via the lymphatics. The inflammation or intoxication must either come by way of the portal vein, which conveys most of the blood supplied to the liver, or through the hepatic artery. As the infective foci in question are located within the drainage area of the portal vein, it is in my view highly probable that this vein is the route by which the toxins come to the liver. This route of infection is therefore possible when either the gallbladder or the choledochus serves as the seat of infection. The part played by choledocholithiasis in the development of hepatitis should accordingly be (in analogy with the encysted gallbladder calculus) a. to impede the flow of bile and therefore to promote biliary infection, b. in its capacity of a foreign body the calculus would serve as a storehouse for toxins and shield them from the protective forces of the organism, and c. by mechanical abrasion on the choledochus mucosa to facilitate transference of the infection to the common bile duct, from which it via the portal vein can reach the lobules.

To the same category as cases of choledocholithiasis with jaundice belong cases of gallstone disease with jaundice caused by some factor other than stone occlusion of the choledochus: 3 of duodenal diverticulum (249, 258, 298) and 1 of lymphadenitis on the choledochus (146) and 4 cases where the choledochus was compressed from outside by malignant tumours (S. 335/43, S. 2505 45, U. 914 49, U. 3826 49). One patient (298) suffered from acute cholecystitis and hepatitis and it could not be decided whether the duodenal diverticulum had taken part in the etiology of the hepatitis. The remaining 2 diverticulum cases and the case of lymphadenitis close to the choledochus exhibited no sign of hepatitis, although they were operated on such occasions after the acute attack of pain when hepatitis is most frequent. In the 4 further cases of gallstone disease, all of them with biliary stasis owing to external compression on the biliary duct, I could not in a single instance find hepatitic lesions in the excised samples. However, all these patients had "quiet jaundice" of 2—3 weeks standing in 2 cases, and 1 month in 2 cases.

f. Hepatitis and Previous Diseases that may have Affected the Liver.

According to the literature, clinical changes are found which are suggestive of hepatic damage in quite a number of different diseases. It being likely that an earlier leasion in the liver might increase its vulnerability to new harmful substances, I have recorded such earlier disorders in patients with and without hepatitis. The result is entered in the appendix. It reveals that the frequency of hepatitis in these patients was 54.9 per cent, as against 32.5 per cent in the remaining Uppsala series. The difference is 28.4 $\pm$ 7.8 per cent.

It should be noted that no patient with any of the diseases in question in the active phase (except migraine, diabetes and myocarditis) was included in my series.

However, since earlier attacks of cholelithiasis must be included among the previous diseases, the result is that the first group will include the majority of patients and the table will be as follows.

Patients with 1 attack and no previous diseases 5/46 = 10.9 $\pm$ 4.6 % hep.
,, ,, > 1 attack or 1 attack and previous disease 99/324 = 30.6 $\pm$ 2.6 % hep.
Difference: 19.7 $\pm$ 5.3 % hepatit.

g. Hepatitis and Medication.

Since hepatitis, as pointed out earlier in chapter V, attains its maximum frequency some days after the attack of gallstone disease, it might be possible that the drugs given the patients in connection with

the attack were responsible for the hepatitis. If so, the analgetics given most patients to dull their pains would be the most likely suspects. However, a large number of patients, even such with hepatitis, received no analgetics, because their pains had abated by the time they were admitted to the hospital. Among 60 of my patients with hepatitis, 31 had received no pain-relieving drug, in half of whom the hepatitis was moderate to severe (++ to +++). The remaining 29 patients had been given analgetics, but only about one third of them had moderate hepatitis (++). Judging by this, it would seem as though administration of analgetics reduces the severity of the hepatitis.

Another sub- stance given patients in connection with an attack of gallstone disease is the contrast medium which in most cases was administered before a roentgenographic examination. In my series, though, about 30 per cent of the patients with hepatitis had been given no contrast medium, which therefore cannot be the sole cause of hepatitis. Analysis of the frequency of hepatitis in patients who had undergone contrast roentgenography of the gallbladder and in patients given no gallbladder contrast medium did not produce a significant difference between the two groups, the respective percentages being 30.2 ± 3 % and 24.4 ± 3.7 %. Difference: 5.8 ± 4.8 %.

A drug comparatively often given to the patients, particularly during the latter half of the investigation, was some sort of sulphonamide preparation. A tabulation of the frequency of hepatitis among the patients during the latter half of the investigation reveals that among those given sulphonamides the frequency of hepatitis is 23/49 or. 47.0 ± 7.1 per cent. Among those given no sulphonamides the corresponding frequency is 38/84 or 40.4 ± 5.1 per cent. The difference is only 6.6 ± 8.7 per cent. Since the most severe cases of inflammation were the ones who usually were given sulphonamides, they might have been expected to manifest a higher frequency of hepatitis. The negligible difference is therefore surprising and more than anything else would seem to suggest that sulphonamides prevent rather than promote the onset of hepatitis.

The anesthetic used at the operation cannot have caused the hepatitis, since even after the strongest liver poisons the onset of hepatitis is delayed by at least 12 hours (Himsworth). Similarly, operational trauma cannot have been the cause of the disorder.

h. Hepatitis and Pain.

Although my investigation mainly has concerned itself with the anatomic changes that are characteristic of acute cholecystogenic hepatitis, I have not felt entitled to neglect an important feature of an attack of acute gallstone disease, viz. the pain accompanying the attack and

the somatic phenomena secondary to the pain. As I am not competent to discuss the relationship between pain and hepatitis in all its implications, I shall remain content to discuss the anatomical basis on which pain is capable of affecting the liver. It is universally held that strong nervous stimuli, e.g. pain, can cause vasoconstriction, and in severe cases shock. Therefore, it is possible that the pain associated with an attack of gallstone disease can affect the liver also via vasoconstriction. In this connection, the general effect on the organism of shock should be kept in mind as well as the local action on the liver. The size of the portal stream is controlled entirely by the systemic blood pressure and the peripheral resistance in the gut. At constant blood pressure the portal stream is regulated by the degree of visceral constriction. The volume of the arterial stream is governed by the tone of the terminal arterioles of the hepatic artery (Howell's Textbook of Physiology 1947). This being so, it is important to know that the lobules of the liver are supplied with arterial blood. The arterial capillaries entering the central sinusoids are especially interesting because it is in this very region that hepatocellular necrosis starts in acute cholecystogenic hepatitis. Furthermore, since it has been found that small ganglion cells or chromaffin cells are present in the neighbourhood of the arterial capillaries, it is highly probable that the latter are contractile. Too, the results of experimental injections into the hepatic artery, which sometimes have filled the central and sometimes the peripheral sinusoids, may be evidence that the arterial capillaries can alter their state of contractility. It consequently is probable that pain can influence the development of hepatitis via the vascular system. There is, however, no obvious correlation, though, between the intensity or duration of the pain and the degree of hepatitis: my series includes patients with extensive hepatitis who had felt little pain and vice versa.

In discussions on pain in combination with an attack of acute gallstone disease, the influence on the liver from high centres, e.g. the basal ganglia, must also be taken into consideration. So, for example, a hypothetical explanation of the cirrhosis associated with the hepatolenticular syndrome (Wilson) is based on a metabolic disorder due to a morbid process in the brain. Since pain is conducted to the thalamus it might be that pain in a manner analogous to that in Wilson's disease can affect the liver.

i. Hepatitis and Temperature.

Since the increase, especially when it is high, in temperature associated with an attack of gallstone disease, might be capable of causing toxic lesions in the liver and thereby promote the onset of hepatitis, I have tabulated the temperature in the cases with and without hepatitis. The result appears in table X.

Table X.

	37°	37—37.9°	38—38.9°	39—39.9°	40°
With hepatitis	3	45	44	11	1
Without hepatitis	9	143	95	40	9

It will be seen that 53.8 ± 4.9 per cent of the patients with hepatitis had a temperature over 38°, whereas the corresponding figure for patients without hepatitis is 52.3 ± 3.0 per cent. The corresponding values for temperature of 39° and up are 14.4 ± 3.4 and, respectively, 17.7 ± 2.3 per cent. Consequently there is no statistical difference between the groups. The temperatures used are the highest measured figures after the attack of gallstone disease.

CHAPTER VI.

Clinical Signs of Cholecystogenic Acute Hepatitis.

As mentioned previously in the chapter on the appearance of hepatitis, the parenchymal lesions are as a rule rather small. Consequently it is unjustified to reckon a priori with any distinct clinical symptoms which are attributable to acute cholecystogenic hepatitis. The coexsistent change in the gallbladder and often in the rest of the biliary system can be made responsible for most of the clinical signs which are present in combination with the gallbladder disorder. Thus, the fever and the leukocytosis as well as the higher sedimentation rate can be due solely to the gallbladder affection, be it bacterial or toxic in origin.

For this reason I think it pointless to look for any deviations in the tests, that can be attributed to hepatitis, since none of the symptoms concerned can be considered specific for hepatic damage. I have none the less compared the sedimentation rates in patients with hepatitis to that in patients without hepatitis. On the basis of the group means for the first week after the attack of acute cholelithiasis there was no difference between the two groups, the figure in both cases being 30 mm.

Even if so called specific liver function tests are used, the comparatively small extent of the hepatocellular damage as compared with the crude distinctions provided by these reactions makes a difference improbable.

When I commenced my investigation, I had no means of predicting its results and therefore did not know at what stage of the disease hepatitis was prevalent. Consequently the liver function tests were not always applied at the best time, particularly not always at the time when

the piece of liver was excised. Therefore, apart from a limited number of cases, I was unable directly to compare the results of the liver function tests and the observations from the liver samples. Furthermore, as emphasized previously, the absence of hepatitis in the sample is no certain indication that the rest of the liver also was free from hepatitis.

The liver function tests used for the purposes of the present investigation were: Hanger's Cephalin-Cholesterol Flocculation Test, Thymol Turbidity Test, and serum bilirubin test. For further details concerning the technique of these tests, the reader is referred to TALLROTH's thesis (Acta Chir. Scand., Supplementum CXLV 1949). The controls used in the interpretation of the tests were also collected from the same work. The control subjects were examined at the same laboratory as my series, and the controls belong to the same geographical population as the patients in my Uppsala series.

The results of *Hanger's test* are entered below. Its customary normal value is designated o to ±. The test being sensitive, its result for severe hepatic damage, such as infectious hepatitis, will most often be 3 to 4 ±. The pathologic limit has therefore often been raised to this level. Hanger's test was applied in 130 cases of my series, a pathological reaction (i.e. + + and up) being obtained in 37 ± 4.2 per cent; and in the control series 18.7 ± 2.6 per cent. The difference is 18.3 ± 5 per cent. If values of + + + and up were considered pathological, a pathologic reaction was obtained in 13.8 ± 3.0 per cent. In the 220 controls a pathological reaction was obtained in only 1.8 per cent. The difference is statistically significant, being 10.6 ± 3.2 per cent.

Maclagan's thymol turbidity test was performed in 138 cases of my series. If values of 4 units and up are considered pathological, only 3 cases showed values over 4 units, i.e. 2.2 per cent; controls 1.7 per cent. On the other hand, if the limit was put at 3 units, 7 cases were pathologic, i.e. 5.1 per cent; controls 3 per cent. It must be taken into consideration, however, that the factors in the blood which bring about the reaction in Maclagan's thymol turbidity test are not produced until some time after the onset of the liver damage, and that the test remains positive much longer than the other liver function tests. As a reaction to the form of acute hepatitis of interest to us here, the thymol test is not very suitable. Furthermore the large majority of tests in my series were taken within the first few days after the attack.

Serum bilirubin test. In my series the bilirubin content of the blood serum was determined in 152 cases of gallstone disease without a demonstrable obstruction in the hepatico-choledochus. As also has been pointed out previously, the patients had no signs of other simultaneous disorders that might have disturbed the function of the liver. The normal bilirubin level is put at 0.1– 1.0 mg % (total). According to this criterion, my series contained 66 pathologic cases or 43.4 per cent. (The frequency of hepatitis in the same group was 43.2 per cent.)

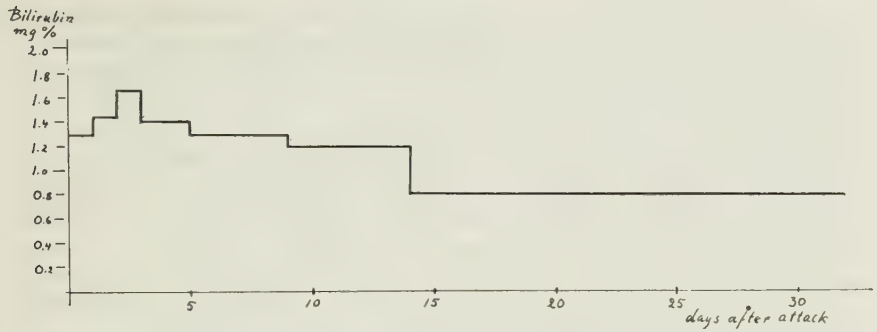

Fig. 12. Average values of serum bilirubin on different days after attack of gallstone disease. (Uppsala series.)

If the mean daily bilirubin value for every day of the 3 weeks' duration of the hepatitis is reproduced graphically, a curve like the one in fig. 12 will be obtained. It will be seen from the figure that the bilirubin value was pathologic for the first 14 days after the attack of gallstone disease, and that it gradually drops to normal values. When the curve of bilirubin values is compared with the curve of hepatitis frequency, it turns out that the bilirubin begins to increase before the hepatitis attains its maximum frequency. With respect to the implications of this circumstance, the reader is referred to the subjoined discussion on the development of hepatitis.

CHAPTER VII.

Discussion and Conclusions.

On the subject of the changes in the liver described in chapter IV, which are seen in association with an attack of gallstone disease, the literature contains but few and vague statements. Most authors who have devoted any attention to the relationship between gallbladder and liver affections have as a rule based their hypotheses concerning this relationship on chronic interstitial hepatitis. Whenever any observations have been made with respect to acute hepatitic changes, they have entered the text more in passing and only been mentioned with a word or two. GRAHAM & coworkers sometimes observed slight necrosis in the lobular periphery but otherwise did not even mention the phenomena due to acute hepatitis; they chiefly interested themselves in the periportal lymphocyte infiltrates. The mortality in the series of TIETZE & WINKLER was so high (36 per cent) that it simply cannot have been an average series — the patients must have been selected. Two of the

described types of liver changes suggest that the parenchymal cells were extensively damaged. However, judging by the descriptions and illustrations of these two types, it probably was a matter of acute infectious hepatitis, which at the time of writing was not recognized as a patho-anatomic entity.

In their studies of the liver in combination with cholecystitis, JUDD & coworkers above all found pericholangitic infiltrates and fibrosis, but they also stated that in some cases they observed hepatocellular damage in the form of poorly stained or small nuclei.

HEYD, KOSTER, GOLDZIEHER & COLLENS, and FLINT have only described the changes caused by interstitial hepatitis and observed no damage to the parenchymal cells.

PETTINARI has chiefly studied interstitial hepatitis and the acute features in the form of abscess formation of the interstitial infiltrates, but he also recorded degenerative hepatocellular changes and fatty infiltration.

According to WILENSKY (1944) necrosis or connective tissue changes in the liver should never have been observed in connection with acute inflammations in the gallbladder.

I have myself in 1944 reported the existence of cellular degeneration and necrosis in connection with the gallstone disease.

In their description of the histological liver changes due to biliary obstruction, POPPER & FRANKLIN stated that in cholelithiasis they had observed polymorphonucleated leukocytes in small areas of focal necrosis.

The infiltrative hepatitis reported by MATEER & coworkers in cholelithiasis and peptic ulcer was said to be characterized by absence of cellular necrosis, despite the fact that it is localized to the parenchymal zones of the liver. Judging by the description and photomicrographs, however, I fell obliged to suspect that it may be a question of the same type of hepatitis as in chapter IV in gallstone disease and as described in my lecture (1948) on peptic ulcer.

In all my cases there was necrosis of parenchymal cells and the pictures were uniform. Naturally, the necrotized cells were present in many different stages of disintegration and they were consequently more or less distinctly visible in the slides. The leukocyte infiltration that takes place in the lobules in connection with acute cholecystogenic hepatitis is always confined to the immediate neighbourhood of the necrotized foci. Only in the very earliest stages of an acute inflammation in the extrabiliar ducts is the leukocyte infiltration visible elsewhere in the lobules. It is localized to the periphery of the lobule and gradually enters into the interlobular tissue. I interprete it as a result of lobular intoxication via the portal blood from an infected focus in the bile ducts. This leukocyte infiltration is not enough to warrant a diagnosis of acute cholecystogenic hepatitis; it is at most an integrated

part of the condition in its initial stages. To speak of acute cholecystogenic hepatitis in my sense of the word, I also demand the presence of necrotized parenchymal cells. On the basis of this definition of hepatitis, earlier observations of acute cholecystogenic hepatitis, will turn out to be very sparse and incomplete.

With respect to interstitial hepatitis in cholecystitis, the observations in the literature are much more numerous and fully described. However, only in so far as the lymphocyte infiltrations occurring in this form of hepatitis can be put in correlation with the gallstone disease, is it permissible to regard this form of hepatitis as cholecystogenic. This relationship will always be difficult to estimate, since not only the importance of currently active but also that of previous diseases for the development of interstitial hepatitis must be taken into consideration. It has been demonstrated that this form of hepatitis can be related to the most varied toxic-infectious conditions in the body, and it is therefore easy to appreciate that the value must be very limited of studies based on the presence of interstitial hepatitis. Moreover, if the lymphocyte infiltrations can arise as a consequence of the normal detoxifying function of the liver (which is most probable), their significance as signs of liver damage becomes even more problematic.

Acute cholecystogenic hepatitis was present in 28.1 per cent of the 370 examined average cases of acute and chronic cholecystitis as well as cholelithiasis and occurred as a consequence of the attack of gallstone disease. During the first few days after the attack, its frequency increases, which suggests that it develops after and not before or at the same time as the attack. If it arose before or together with the attack of acute gallstone disease, the acute hepatitis ought to be more frequent nearer the attack than the other way round. Having taken samples on only one occasion from each patient, I cannot state anything definite concerning the duration of the liver disorder. Nevertheless, since the hepatitis only occurred with any frequency worth speaking of for 3 weeks after the attack of gallbladder disease, the maximum duration probably is about 3 weeks. Various factors related to the resistance of the patient to the toxins causing the hepatitis may interfere and delay or expedite the process. The harmful substances may be of varying toxicity, the liver may be more or less vulnerable, and the circulation may be variously affected in the individual patients. It is doubtful, therefore, if any conclusions concerning the resultant liver lesions can be drawn from the intensity and duration of the attack of cholelithiasis. In some cases I have seen considerable hepatitic changes after very moderate attacks, and in some other cases where the attack was very severe I found no lesions whatsoever in the liver.

If, on the basis of the results of the present investigation, an attempt should be made at naming the factors in the acute attack of cholelithiasis which influence the hepatitis, it is obvious that the most important

is the inflammation of the gallbladder as it appears in the microscopic section. And, evidently, the inflammation in the gallbladder wall with consequent reaction on the part of the small veins has the greatest influence in this respect. On the other hand, it seems to make little difference whether or not the bile is infected, but only the extent to which the wall is affected by the inflammatory process. Moreover, it is only by way of the gallbladder wall that the toxic products are capable of reaching the portal vein and penetrating the liver. The first microscopic signs of intoxication of the liver are exhibited by the periphery of the lobules, where as soon as the first day after the acute attack leukocyte accumulations are visible, especially around the biliary canaliculi. It is the same region that in general infections with staphylococci and streptococci exhibits the strongest hepatic reaction (Bahrmann's "Ausscheidungscholangitis").

The central intralobular necrosis typical of cholecystogenic hepatitis becomes frequent somewhat later. Its genesis in toxic hepatitis has been explained by Himsworth, and the observations made in my investigation agree with that explanation. According to Himsworth, toxic agents reach the liver via the blood, which first gets to the peripheral parts of the lobules. There, the toxic effect will consequently be greatest and as the blood is detoxified while passing through the sinusoids the content of toxins decreases, until the blood is sufficiently pure to reenter the systemic circulation. The toxins may cause hepatocellular swelling so that the sinusoids are compressed. This process predominantly takes place peripherally in the lobules where the blood contains the highest amount of toxic products. The consequent reduction of the intralobular circulation of blood has the effect that the central part of the lobules will be supplied with little, if any, of the blood constituents essential to hepatocellular life. Hepatocellular destruction is not only caused by oxygen deprivation (for adequate supplies should be available from the arterial capillaries entering the central sinusoids), but also by a lack of nutrients vital to hepatocellular metabolism. For, by means of animal experiments, it has been shown that toxic hepatitis as caused by carbon tetrachloride can be prevented by adminstration of hypernormal amounts of certain nutrients not later than some hours after the intoxication. These substances are amino acids containing sulphur (e.g. cysteine and methionine). Accordingly, in my investigation, the role of the intoxication for the development of hepatitis would seem to be the following. When the gallbladder is the seat of an inflammatory process, the blood takes up toxins and perhaps bacteria which are carried along through the branches of the portal vein to the liver. The peripheral parts of the lobules react first, with hepatocellular swelling and perilobular inflammation. This compresses the sinusoids so that the circulation, especially with respect to certain nutrients, becomes inadequate in the central parts of the lobules, where cellular destruction results.

Although the inflammation in the wall of the gallbladder thus seems to be the crucial factor in the genesis of hepatitis, some contributory factors exist. They are found partly in the gallbladder and/or bile ducts and partly in the liver itself. Concrements in the biliary ducts are important for the development of the inflammatory process. They may both cause stagnation in the flow of bile, thereby promoting bacterial growth in the stagnant fluid, and, being foreign bodies, provide a foothold for bacteria. Moreover, concrements lodged in narrow passages (usually the neck of the gallbladder and in the papilla of Vater), may lesion the mucosa by subjecting it to pressure, whereby the infection will have an entry to surrounding tissues. Epithelial lesions of this kind provide an outled for fluids which are toxic to the tissues and are normally present in the bile ducts (bile and pancreatic juice). Even if these fluids, or the products formed in them by the lesioned tissues, do not directly damage the liver in the same manner as bacterial and certain other toxins, the lesioned tissue may become a suitable growth-promoting substrate for bacteria. A number of authors have demonstrated that the bacteria which are found in cholecystitis almost without exception belong to the bacterial flora of the intestine and therefore are capable of growing in a substrate containing bile. Besides biliary calculi, other factors may promote the onset of an inflammatory process in the biliary ducts. Changes in the form of muscular destruction in the gallbladder wall and fibrosis which make the wall rigid are the chief causes of impaired gallbladder contractility. What has been said on the subject of gallbladder changes is in similar cases true of the choledochus.

My investigations have on the other hand provided no support for the assumption that pancreatic affections or biliary stasis as such, i.e. without infective complications, can be important factors in the development of hepatitis.

According to the investigations reviewed in the chapter on the development of cholecystitis, the disorder was of bacterial origin in about 1/3—1/2 of the cases. This figure agrees well with the frequency of hepatitis among my cases, particularly among those assembled at the University Hospital, Uppsala, among which hepatitis was demonstrated in 46.2 per cent.

If we now turn to the liver itself and consider what intrahepatic factors are favourable for the onset of hepatitis, two interesting circumstances emerge. One is the higher frequncy of hepatitis among the Uppsala patients operated on during the winter season. A plausible reason is that the liver cells undergo some change during the winter season. In summer the food is rich in carbohydrates and in winter it contains more fats. Probably, therefore, the liver cells are affected by this difference in diet. According to Davis & Whipale, and Opie & Alford, the susceptibility of the liver to chloroform intoxication is increased by a fatty diet and reduced by one rich in carbohydrates.

Even if fatty infiltration alone is not enough to produce hepatitis, it does make the liver cells more vulnerable to toxic action. Another factor that may influence hepatocellular resistance is whether the patient previously has had diseases known to be capable of lesioning the liver. It has been shown in the present investigation that toxic hepatitis attendant upon an attack of gallstone disease heals without leaving any traces in the hepatocellular structure. The damaged liver cells are regenerated, a phenomenon that is very characteristic of the liver. In the chapter on hepatitis and previous diseases, it appeared that the frequency of hepatitis might be higher in patients who had had and recovered from diseases known to be capable of causing liver damage than in patients who had not had such disorders. It also appeared that on the average the frequency of hepatitis seemed to be higher after several attacks of gallstone disease than after the first attack.

Both these considerations may indicate that such liver cells as have previously been lesioned are less resistant to new onslaughts of harmful factors, just as the findings in chloroform intoxication.

The assumption that the resistance of a damaged and healed liver is lowered is borne out by the common clinical observation that a person whose liver has been damaged, usually by infectious hepatitis, gets manifest jaundice in connection with reintoxication, e.g. from appendicitis. Such jaundice, however, as a rule vanishes without leaving any evidence that the first disease had brought on cirrhosis of the liver.

Two phenomena suggestive of hepatitis were pointed out in the chapter on clinical symptoms of cholecystogenic acute hepatitis. One was a slight bilirubin increase of the same frequency as hepatitis in my series of patients. The maximum bilirubin level was recorded during the very first days, i.e. before the greatest frequency of hepatitis, and it slowly dropped during the next two weeks or so. If it is desired to relate this bilirubin increase to the hepatitis, it may be said that it sets in during the initial stages in the development of the hepatitis, when the latter is manifested by intoxication of the lobular periphery which then exhibit hepatocellular swelling and compressed sinusoids. At the same time, it should be expected that the hepatocellular swelling compresses the biliary capillaries in the lobular periphery, resulting in central intralobular biliary stasis (the centre of the lobule being the main seat of bile production). The time for the bilirubin increase, therefore, agrees well with the theory concerning the development of hepatitis. The other clinical symptom of hepatitis was a positive Hanger reaction, and in my series the positive tests had the same frequency as hepatitis. Hanger's reaction is considered a sign of immunization action in the organism against the infection. Hanger's test, therefore, seems to confirm the hypothesis that, cholecystogenic acute hepatitis is caused by the toxic agents emanating from a source of infection.

CHAPTER VIII.

Summary.

A review of earlier observations concerning liver changes in connection with gallbladder affections, and a survey of different opinions with respect to the development of cholecystitis, is followed by a description of the liver's microscopic appearance and structure as well as the intrahepatic circulation. In this connection, the different routes by which the infection can reach the liver are discussed and debated. From this, I have been lead to the conclusion that the liver is infected mainly via the portal vein.

In 370 patients with gallbladder affections, predominantly acute and chronic cholecystitis as well as cholelithiasis, I have, at operation, excised one or two pieces from the liver and examined them microscopically. As controls I used similar samples excised from 30 patients with gallbladder affections in the latent stage. The study was performed through the years 1942—1946 at Sundsvall Hospital and 1946—1949 at the Surgical Clinic of the University Hospital, Uppsala. The studies produced the follwing results.

A. There exists an acute form of cholecystogenic hepatitis belonging to the toxic-necrotic group. It was definitely related to the acute attack of gallstone disease. Its frequency in the combined series was 28.1 per cent, in the Sundsvall series 16.4 per cent and in the Uppsala series 46.2 per cent. The difference between these groups is 29.8 ± 4.8 per cent. (Owing to duplicate determinations the number of patients with hepatitis in the Uppsala series should be increased by 7, and when these are deducted the difference will be 25.0 ± 4.8 per cent.) The difference between the groups may in part be due to dissimilar criteria for operation, but other reasons are much more likely. Differences in the constitution and nutrition of the populations have been advanced as possible reasons, particularly the fact that the Sundsvall series was assembled at a time marked by shortages and rationing and, therefore, less chances of overnutrition.

B. The hepatitis has exhibited no correlation to the age or sex of the patient.

C. The hepatitis could not be attributed to the contents of the gallbladder as found at operation, but it was very closely correlated to inflammatory changes in the gallbladder wall.

D. Pancreatic complications of the gallstone disease did not increase the frequency of hepatitis.

E. Whenever the gallbladder affection was combined with complications from the choledochus, the frequency of hepatitis was higher, but the difference between the frequencies with and without choledocho-

lithiasis was merely 11.8 ± 5.1 per cent. In connection with this complication, the subject of cholangitis and the route taken by hepatic infections were discussed. I have emphasized that in my series there was no anatomic evidence suggesting that the cholangitis usually was of the ascending type.

F. Previous gallstone attacks or previous diseases ordinarily assumed to affect the liver make the latter more susceptible to renewed attacks of hepatitis. This is statistically significant.

G. Drugs (in my investigation chiefly Eucodal), that were given to the patient to alleviate the pains of the gallstone attack, did not seem to increase the morbidity of the hepatitis, nor did sulphonamides or any of the contrast agents given the patient for purposes of cholecystography have any deleterious effects on the liver structure.

H. The significance of pain in connection with the attack of gallstone disease is discussed, but it seems certain that it at least cannot be the only etiologic cause of the hepatitis.

I. The rise in temperature attendant upon an acute attack of gallstone disease did not increase the frequency of acute cholecystogenic hepatitis.

K. As a rule the form of hepatitis in question is not very extensive and gives rise only to slight clinical symptoms, most of which are obliterated by the inflammatory symptoms of the changes in the gallbladder. Hanger's reaction, however, was positive in a greater number of cases after gallstone attacks then in a normal series. The positiveness of the thymol test, though, was not significantly greater. The serum bilirubin showed a slight increase during the first days after an attack of gallstone disease, which I attribute to heptatocellular swelling in the lobular periphery during the initial stages of the hepatitis.

Material and Controls.

No.	Diary No.	Age & Sex	Diagnosis	Fatty infiltration	Glycogen Content	Lymphocyte infiltration	Hepatitis	Gallbladder Contents	No. of attacks	Op. day. (Days between attack and operat.)	Meulengracht s. Bilirubin	Diastase	Roentgenographic Result	Temp.	Sedimentation Rate	Thymol test	Hanger test	Para	Course	Micr. app. of Gallbladder	Simultaneous Diseases	Previous Diseases
1	1437/42	61 f	c+	–	++	++	–	–	1	9	62	4	–	37.6	23			8	16†	–	5	9
2	1815	41 f	c	+	+++	–	–	1	10	16	8	8	R–	37	8			1	10	-	12	
3	1569	56 f	ca	–	+++	++	–	3	5	4	14	4	–	39.4	27			–	†		5	
4	1620	37 f	ca	–	+++	++	–	–	20	7	6	4	R+	38.2	6			6	†	–		
5	1682	44 m	cc	++	+++	–	–	–	3	6	7	6	R–	37.6	3			–	–	–		
6	1826	47 f	ca+	+	+++	++	++	1	20	2	62	4	–	38.4	12			–	–			
7	2521	57 f	ca	++	+	+++	+	–	50	6	25	8	–	38.3	28			3	–	–		
8	2585	45 f	ca	+	++	+	–	1	10	6	32	5	R+	38	8			1	–	–		14
9	2646	51 f	ca	+++	+	+++	–	3	3	3	14	4	R+	39.4	13			–	–	-		
10	2654	25 f	cc	–	++	–	–	–	1	16	10	10	R–	37.5	14			1	–	-		
11	2739	33 f	ca+	–	++	+++	–	3	10	6	25	10	–	37.9	26			1	–	-		
12	2746	40 f	ca	+	++	++	–	–	2	4	15	8	–	38.6	37			1	–	–		
13	2806	53 f	cc	+	+	–	–	–	20	11	10	4	R+	38.2	14			–	–	–		
14	2847	56 m	ca	+	++	+	–	1	1	60	8	3	R+	38.6	14			–	–	–		
15	2861	73 m	c	–	+++	–	–	1	100	23	10	10	R–	37.5	4			–	12†	–		18
16	3025	20 f	c	–	+++	–	–	–	14	13	4	6	R–	39.3	17			1	–			
17	3051	35 f	ca	+++	++	+	–	1	3	2	4	4	–	37.5	50			0	20	–		
18	3069	57 m	ca	++	+	+	–	–	1	17	8	3	–	38.6	31			–	–	–		
19	3113	53 f	c	–	+++	+	–	–	20	4	4	4	R–	37.8	18			–	–		5	
20	3155	44 f	c	+	+++	+	–	–	1	8	12	2	R–	37.3	5			5	–			21
21	3374	35 m	cc	–	++	+	–	–	10	2	11	4	R–	37.2	2			–	–	–		
22	3656	55 f	ca	+	+	++	–	1	5	2	10	3	–	38.2	7			–	10	–		
23	161/43	48 f	ca	+	++	+	–	–	20	12	10	5	–	38.1	6			–	–		5	5
24	173	70 m	ca	+	+	+	+	–	1	7	18	5	–	38.2	3			–	–		5	5
25	425	64 f	ca	+	+	++	–	–	3	5	10	6	–	38.4	72			–	–			
26	534	52 f	ca	+	+++	++	–	–	1	2	–	–	–	37.9	19			5	–	–		
27	676	42 f	c	–	++	++	–	–	10	6	6	4	–	37.8	7			–	–			
28	756	69 f	cc+	+++	++	++	–	–	700	11	11	6	R+	38.5	4			–	20†			
29	814	59 f	ca	+	+	+++	–	–	2	5	10	4	–	39	5			–	–			
30	829	68 f	ca	++	++	++	–	–	100	10	6	3	R+	39.2	30			–	–			
31	832	37 f	c+	–	+	–	–	–	2	4	22	3	R+	38.1	9			3	–	–		
32	1015	44 m	ca	+	++	+	–	–	1	6	14	5	–	39	4			–	–	–		
33	1102	54 f	ca	++	+++	+	–	–	1	7	7	3	R+	38.2	12			–	–	–		
34	1145	32 f	cc	–	+++	+	–	–	2	6	15	7	R+	37.6	34			2	–			
35	1158	75 f	cc–	–	++	++	–	–	2	24	26	6	R–	38.8	57			–	10		5	12
36	1281	58 f	ca	–	+	++	–	–	40	11	45	6	–	38.6	116			–	5†			5
37	1287	65 f	ca	+++	++	++	++	–	30	5	7	5	R+	37.6	18			–	–			
38	1306	50 f	ca	–	+	+	–	–	2	4	5	6	–	39.4	69			–	–			
39	1376	49 f	ca	++	++	++	–	–	50	6	–	4	R+	38.1	6			–	–		5	17
40	1418	57 f	cc+	+	+	++	+++	–	2	10	60	5	R+	37.6	29			–	–	–		3
41	1480	53 f	ca	–	++	++	–	–	1	18	11	6	R+	40	76			–	–			12
42	1483	39 f	cc	–	++	+	–	–	10	8	12	7	R+	37.9	12			–	–			13

No.	Diary No.	Age & Sex	Diagnosis	Fatty inf.	Glyc.	Lymph. inf.	Hepatitis	Gallbl. Cont.	Attacks	Op. day	Meul. s. Bil.	Diastase	Roentg. Result	Temp.	Sed. Rate	Thymol	Hanger	Para	Course	Micr. app. of G.	Sim. Dis.	Prev. Dis.
43	1487/43	43 f	cc	++-	- -	- +		–	1	6	8	3	R+	37.5	13			–	–			
44	1598	55 f	ca	++	+++	++	–	1	1	14	–	5	R	38.4	17			6	–			
45	1689	30 f	ca	+	+++	+	–	–	2	2	2	7	–	38.4	12				–			
46	1695	24 f	c+	–	+++	–		–	3	7	9	10	R	37.3	17			–	–			
47	1838	66 f	ca	+	+++	++	–	1	1	20	9	4	R+	39	9			7	–			
48	2076	54 f	c	+	+++	–	–	–	20	18	7	5	R+	37.8	9			–	–			
49	**2115**	**23** f	c	+	++	+			**4**	**50**	**10**	**6**	–	**37.6**	**7**			**0**	–			
50	2152	53 f	cc	++	+++	–	+	–	3	10	8	10	R	38.7	65			–	–		5	
51	2185	69 f	cc	++	++	+	+	–	2	2	5	4	-	37.6	28			–	–		5.2	
52	2187	66 m	cc–	–	+++	+	–	–	2	35	–	–	R	38	36			–				
53	2202	72 f	cc+	+	+++	++	–	–	20	15	50	9	R+	37	20			7	5†		5	
54	2243	23 f	c	–	+++	-	–	–	3	6	12	–	-	37	10			0	–			
55	2287	61 m	ca–	+	+++	+++	+	–	4	1	–	–	–	38.6	16			–	–		8	
56	2293	69 m	ca+	++	++	++	–	–	5	2	70	7	–	38.8	65			–	5†		5	
57	2318	38 m	ca	–	+++	+	–	–	1	5	10	3	R+	37	4			–	20†			12
58	2419	22 f	cc	–	+	+	–	–	3	3	54	3	–	37.4	16			1	–			
59	2428	65 f	ca	++	+	++	–	–	4	4	6	5	-	39.3	46			–	–			
60	2473	48 f	cc+	–	+++	–	–	–	8	10	96	5	–	39.5	61			6				
61	2502	57 f	c	+++	+++	+	+	–	3	4	10	3	–	37	15			–	–			2
62	2528	33 f	ca	++	+	–	–	1	3	13	-	10	R+	38	–			1	16†			15
63	2564	45 f	cc	+	++	+++			15	11	8	6	R+	38.1	54			3	–			
64	**2678**	**57** f	c	–	++	+	–	–	**10**	**35**	**5**	**5**	–	**37**	**21**			–				**12**
65	2711	62 f	c	+	++	–	–	–	4	22	7	10	R	38.5	4			3	-			
66	2815	23 f	ca	–	+	-	–	–	1	4	4	6	R	37.9	17			-	–			12
67	3003	42 f	ca	–	++	–	–	–	6	1	6	5	–	38.6	37				-			12
68	3109	43 f	ca		+	.	–	–	1	1	8	3	–	38.1	18			–				
69	3165	32 f	ca	+	++	+	–	–	40	20	–	–	R–	37	3				–			12
70	3226	59 m	c	+	+++	–	–	–	1	9	11	4	R	37.2	16				–			
71	3234	43 f	ca	–	++	++	+	–	3	8	4	4	R	39	121			–				17
72	3325	57 f	ca	+	++	+	–	–	1	6	6	3	R	37.6	3			–	5†		5	8
73	3430	42 f	c+	:	+	-		–	1	8	36	3	–	37.1	15				–			6
74	3433	65 f	c	–					1	16	5	2	R	37.8	34			–	–			12
75	3785	33 f	cc	–	++	++	–	–	10	7	5	6	R	38.7	33			2				
76	3863	35 m	c	–	+-+				2	8	6	5	R	37.4	4			–	-			
77	3963	65 f	ca	–	+++	+	–	–	2	2	3	5	–	39.3	8				-			
78	4049	53 f	ca+	–	+	++	–	3	10	5	6	4	-	38.6	48							
79	47/44	45 f	ca	++	+	++	–	–	2	7	6	5	R	38.0	8			–				12 19
80	65	57 f	ca	+	++	+ -	–	–	15	10	14	6	R	38.3	00			-				
81	112	53 f	ca	++	++	+	+	3	4	2	–	5		38	51			-				
82	288	55 f	ca	+	+++	++	–	1	15	9	6	4	R	37.4	0							
83	334	44 f	c	++	+++	++	–	–	1	26	–	–	R–	37.1	28							
84	396	44 f	c	+++	+++	++	–	–	1	22	4	7	R	37.5	34			–			5	11
85	515	24 f	c	+	+-+	+	–	–	6	14	9	5	R	37.5	6			1				
86	541	44 m	ca	–	++	++	–	–	20	5	36	4	R	37.5	8			–	-			12
87	544	41 f	cc	+	++	+	+	–	10	6	13	6	R	38.0	63			-				
88	559	60 m	cc	++	++	+	–	–	1	10	7	5	R	37.1	17				–			12
89	**589**	**57** f	c	++	+++	+	–	–	**20**	**50**	**12**	**3**	–	**37.8**	**10**				–		5	**15**
90	612	39 f	c	+	++	–	–	–	1	7	10	4	R	37.5	18			5	-			19
91	653	34 m	cc	–	+++	++	–	–	7	9	11	5	R	38.2	8				10			

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92	655/44	48 f	c	++	++	–	–	–	1	25	6	6	R–	37.3	7			2	–			
93	756	25 f	c	+	+++	+	–	–	20	5	6	8	R–	37.3	4			1	–			
94	795	29 f	c	+	+++	–	+	–	5	8	7	3	R–	37.6	11			–	–			
95	**857**	**44** f	c	–	+++	–	–	–	**2**	fr.	**2**	**6**	R+	**37.9**	**10**			–	–			**12**
96	968	36 f	ca–	+	++	++	–	–	1	11	9	4	R+	37.5	18			–	–			
97	999	28 m	cc	–	++	+	–	–	20	2	6	4	R+	36.2	4			–	–			
98	1004	55 m	ca	+	++	++	–	–	1	11	8	5	R+	37.6	23			–	†		5	
99	1036	37 f	cc	–	++	+	–	–	20	15	7	5	R+	36.9	11			–	–			
100	**1069**	**54** f	cc	+	+++	–	–	–	**40**	**100**	**6**	**4**	–	**37.4**	**8**			–	–		**5**	
101	1085	60 f	ca	+++	++	+	–	1	150	20	6	6	–	37.1	18			1	–		5	
102	1097	39 f	cc	++	+++	++	–	–	5	9	30	10	R+	38.6	9			–	–			
103	1203	60 f	c	–	+	–	–	–	1	15	44	10	–	37.1	12			–	20†		4/5	
104	1231	30 f	c	–	+++	–	–	–	10	17	16	10	–	37.3	7			1	–			
105	1240	44 f	c+	+	++	–	–	–	100	7	6	2	–	37.9	10			–	–			
106	1274	32 f	ca	+	+++	++	–	1	30	6	7	4	R+	37.5	10			–	–			
107	**1288**	**42** f	c	+	+++	–	–	–	**100**	fr.	**6**	**3**	–	**37**	**48**			**3**	–			**10**
108	1328	60 f	c	+	++	+	–	–	7	2	9	4	–	37.4	9			7	–			
109	1335	49 f	cc	+	++	+	+	–	26	14	11	4	R+	37.3	20			–	–			
110	1442	69 m	ca	–	++	++	–	3	2	9	5	5	R+	37.3	62			–	–			
111	1454	54 m	c	++	+++	–	–	1	10	8	7	4	R–	37.3	5			–	–			12
112	1456	62 m	ca	–	++	++	+	–	1	4	8	5	–	38.8	38			–	–			17
113	1489	54 m	ca	–	++	+	–	–	8	5	7	5	R+	37	32			–	–			
114	1492	58 f	cc–	+	+++	+	–	–	100	24	60	8	R–	38	31			–	–			
115	1522	56 f	ca	++	++	++	–	1	10	9	9	6	R+	38.3	11			–	–		5	5/12
116	1547	57 f	c	++	+++	–	+	–	70	10	10	3	R–	36.9	8			–	–		5	5
117	1573	31 m	c	–	+++	+	+	–	6	6	18	10	R+	37.6	42			–	–			
118	1591	69 f	c+	+	+++	++	++	–	50	16	30	5	R+	38	33			–	5†		5	
119	1632	64 m	ca	–	+	–	–	–	15	14	36	6	–	37.4	50			–	–		5	7
120	1636	50 f	cc	–	+++	+	+	–	2	9	10	4	R+	37	33			–	–			
121	1733	30 f	ca	–	+++	–	–	1	1	5	20	5	R+	37.5	16			–	–			
122	1738	33 f	c	+	+++	–	–	–	5	28	6	5	–	37.3	6			–	–			
123	1801	59 m	ca	+	+++	–	–	1	1	1	–	–	–	38.7	30			–	–		5	15
124	1846	45 f	c	–	+++	–	–	–	6	7	9	6	R–	37.6	9			–	20		5	
125	1853	47 f	ca	+	++	–	–	–	1	6	8	6	R+	37.8	15			–	–		5	20
126	1875	40 m	ca	–	++	++	–	1	2	10	10	4	R+	37.8	51			–	–			
127	**1942**	**62** m	cc	++	+++	–	–	–	**4**	**45**	**9**	**4**	R–	**37.2**	**12**			–	–			
128	1980	63 f	cc	++	+++	+++	–	–	1	8	16	3	R+	37.4	60			–	20		5/21	21/2 15
129	1981	71 m	ca	++	++	++	–	3	1	3	11	5	–	37.7	8			–	7†			
130	1986	64 f	cc	++	+++	–	–	–	1	9	5	3	R+	37.6	4			–	–		5	
131	2052	45 m	ca+	–	+	++	–	–	2	2	–	–	–	37.8	–			–	–			
132	2137	42 f	ca	++	++	+	++	1	2	3	22	8	–	37.1	6			–	–			
133	2216	29 m	cc+	+++	+	+	++	–	3	7	75	5	–	37.9	14			–	–			12
134	2249	57 f	cc+	++	+++	+++	++	–	5	16	15	8	R+	37.7	44			–	–			12/11
135	2314	27 f	cc	–	++	+++	–	–	4	2	5	5	–	37.6	48			2	–			
136	2462	65 f	ca	–	+++	+	–	2	1	8	11	6	R+	39.2	50			–	–		5	
137	**2620**	**35** f	cc	++	+++	–	–	**1**	**2**	**50**	**9**	**5**	R+	**37.8**	7			–	–			
138	2670	42 f	cc–	+	+++	–	–	–	1	5	5	4	R+	37.2	6			–	–			
139	2744	37 f	ca	–	+++	–	–	–	1	2	5	–	–	38	97			–	†			
140	2787	44 f	ca	–	+++	–	–	–	18	11	5	5	R+	37.5	37			–	–			20

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141	2798/44	53 f	ca	–	++	+	+	1	3	22	5	5	R+	37.8	6			–	–			
142	2832	50 f	c	–	+++	+	–	–	3	13	20	10	R+	38	13			–	–			
143	2871	62 f	cc	+	+++	++	–	–	6	20	38	10	–	38	36			–	20			
144	2996	34 f	c	–	++	+	–	–	5	14	15	4	R+	37.6	7			–	20			
145	3020	27 f	c	–	++	+	–	–	2	10	40	5	R+	37.8	38			1	–			
146	3177	42 f	ca	++	++	+++	–	–	1	18	44	4	R+	37.4	18			–	–			12
147	3248	25 f	ca	–	++	–	+	1	2	8	14	5	R+	37.6	14			1	–			
148	3540	52 f	ca	+++	+	++	–	–	2	2	17	10	–	38.3	19			0	–			
149	3619	49 f	ca	–	++	+	–	–	2	8	39	5	–	38.1	68			–	–			13
150	3629	30 f	cc	–	–	+	–	–	6	9	30	6	R+	37.8	13			1	9†			
151	3714	60 f	c+	+	++	+	–	–	30	7	51	10	–	39.5	65			3	–		5	
152	**259/45**	42 f	cc	+	+++	–	–	–	15	fr.	**5**	**3**	R+	**37.7**	31			–	–			
153	528	56 f	ca	++	++	++	–	1	20	7	5	4	R+	37.9	25			–	–			(3)
154	854	66 m	cc+	–	+	+	–	3	15	7	16	5	–	39.1	35			–	7†			
155	898	43 f	ca	+	++	–	+	1	20	9	7	3	R+	37	38			–	–			12
156	904	63 f	ca	++	–	+++	+	3	1	6	12	4	–	38.5	7			–	16†		6	6
157	**914**	**39** f	cc	+	++	+	–	–	**3**	fr.	**6**	**4**	R–	**36.9**	**3**			–	–			
158	1069	27 f	c+	+	++	+	–	–	10	7	6	5	R–	37.3	6			–	–			(12)
159	1080	34 f	ca	–	+	+	–	1	1	3	6	6	–	38	5			0	–			(3)
160	1196	62 f	ca	+++	+++	++	–	3	1	4	17	4	–	38	20			1	–			
161	1197	64 f	ca	+	+++	+++	–	1	1	14	6	2	–	39.3	38			3	–		5	$\frac{4}{5}$
162	1202	52 f	cc	+	+++	–	–	–	20	11	17	4	R–	37.8	5			1	–			19
163	1267	41 f	c	–	+++	–	–	–	10	13	8	8	R+	38	12			1	–			
164	1297	36 f	ca	–	+++	+++	–	1	1	8	6	4	–	38.5	105			2	–			$\frac{14}{12}$
165	1339	46 f	c	+	+++	+	–	–	3	10	17	10	R+	38	35			–	–			
166	1369	66 f	ca	++	+++	++	–	3	3	1	36	4	R–	37	18			–	–		5	12
167	1440	53 f	c	–	+++	+	–	–	3	10	11	8	R–	37	7			–	–			12
168	1457	61 f	c+	+	+++	+	–	1	10	15	13	10	R–	40.4	70			–	1†			
169	1492	55 f	cc	++	+++	+	–	–	20	33	4	3	–	37.6	14			–	–			
170	1506	57 f	ca	+	++	+	–	–	2	4	4	3	–	38.8	23			–	–			
171	1531	54 f	ca	++	+	+++	–	–	1	2	7	3	–	38.2	32			–	–			9
172	1548	47 f	c+	+	+++	+	+	–	6	9	15	5	R+	38.5	5			–	–			
173	1692	57 f	ca	–	+++	+	–	1	2	10	5	4	R+	38.9	10			–	–		5	19
174	1825	50 f	cc+	+	+++	–	–	–	2	20	72	7	–	38.7	42			5	–		5	
175	1924	60 f	ca	++	+++	–	+	1	100	1	5	5	–	37.4	31			–	–		5	
176	2086	49 m	ca	++	+++	++	+	2	150	10	5	4	R+	37.5	20			–	–			
177	2239	62 f	ca	+	+–	+	–	–	2	1	–	5	–	39	46			–	–			
178	2258	58 f	ca	+	+	++	–	1	1	8	–	3	–	40	101			4	–		5	17
179	2295	59 f	ca	++	–	+++	+	3	1	2	9	4	–	38.2	13			–	–		5	
180	2360	50 f	cc+	–	+	++	+	–	3	11	66	5	–	38.5	48			–	–			
181	2456	65 f	ca	–	+++	++	–	3	2	8	9	4	R+	38.6	38			–	–			9
182	**2593**	**58** f	c	+	+++	+	–	–	**1**	fr.	**5**	**5**	R+	**38.7**	**108**			–	–		**15**	
183	2602	53 f	ca	++	+++	+++	–	1	20	11	5	6	R+	39.1	40			–	–		5	
184	2725	61 m	cc	+	++	++	–	–	2	4	–	5	R+	39.2	30			–	–			8
185	2898	59 f	c	+	++	–	–	–	10	8	7	6	R–	38.8	–			–	–			
186	2987	34 f	cc	+	++	+	–	–	2	30	20	10	–	39	25			1	–			
187	3008	62 f	ca	++	+++	++	–	2	1	16	7	5	–	39.7	80			2	–		1	
188	**3240**	**52** f	cc						**1**	fr.	**7**	**4**	R	37				–	–			
189	3588	38 f	c	+	+++	+	–	–	5	21	39	10	R+	37.7	11			–	–			

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190	3620/45	68 f	ca+	+++	+	++	–	3	2	3	8	5	–	38	29			3	7†		[illegible]	
191	3644	44 f	c+	–	+++	–	–	–	4	15	9	4	R+	37.5	2			6	–			
192	3697	51 f	c	+	+++	+	–	–	3	10	6	4	R–	37.4	12			4	–		5	
193	**3755**	**27** f	c	+	+++	++	–	–	**0**	fr.	–	–	–	**37.5**	10			**3**	–		**21**	
194	**3780**	**41** f	c	+	+++	+	–	–	**0**	fr.	–	–	R–	**37.4**	**30**			**1**	–			
195	3793	54 m	ca	++	++	++	–	2	1	13	7	5	R+	38.5	11			–	–		5	1
196	3819	60 f	cc	++	+++	+	–	–	10	9	22	10	R+	38.8	34			–	–			
197	3890	31 f	c	–	+++	–	–	–	3	9	5	8	R–	37.1	5			–	–			
198	3906	51 f	cc	–	++	+	–	–	8	7	7	4	R–	38	22			–	–			3
199	3911	52 f	ca+	+	++	+++	+	2	12	6	4	3	–	38.1	22			–	–			
200	3917	48 f	cc	+	+++	–	–	–	3	8	6	5	R+	37	–			–	–			12
201	3931	53 f	c	++	+++	++	–	–	20	25	9	10	R–	37.4	71			12	–			
202	3934	29 f	ca	–	++	++	–	2	1	2	4	4	–	37.8	28			2	–			14
203	4032	36 f	ca	+	+	+++	–	3	15	3	7	5	–	38.9	10			0	–			
204	4068	40 f	cc	–	++	–	–	–	2	5	5	4	R+	36.8	10			–	–			
205	**4083**	**73** m	ca	–	++	+	–	**3**	**10**	**60**	**6**	**4**	–	**40**	–			–	–			
206	**4093**	**48** f	c	+	+++	+	–	–	**2**	**42**	**5**	**10**	R+	**37.1**	20			–	–		**5**	
207	4105	51 f	ca	++	+++	++	–	–	1	3	7	4	–	38.8	7			1	–			
208	4139	68 m	cc+	+	+++	+	–	–	2	13	7	4	R+	36.9	16			–	–			
209	4206	62 m	ca	–	+	++	–	2	3	8	7	4	R+	39	108			–	–			
210	4219	52 f	ca	++	+++	+	–	3	2	1	7	2	–	38.2	33			5	–			
211	4229	33 f	ca	+	++	++	–	–	3	5	7	4	R+	37.6	35			–	–			8
212	4255	62 f	ca	+	+	++	–	3	1	3	9	5	–	39	32			–	–			12
213	178/46	46 m	c+	+	+++	++	–	–	2	17	50	8	R+	36.4	1			–	–		5	8
214	254	47 f	c+	++	+++	++	+	–	3	10	5	6	R+	37.6	3			–	–			
215	**452**	**25** f	c	–	+++	–	–	–	**1**	**46**	**5**	**3**	R–	**37.2**	**6**			**1**	–		**2**	
216	617	50 f	ca	++	+++	+	–	–	2	10	13	6	–	38.3	49			–	–		5	17
217	660	32 m	ca	–	+++	+++	–	–	10	11	4	2	–	36.3	10			–	–			
218	888	38 f	c	+	++	–	++	–	1	17	42	4	–	37	5			–	–			
219	916	30 f	ca	–	+	+++	–	2	10	3	7	5	R+	37.4	3			–	–			
220	993	61 f	cc+	–	+	+	–	–	3	14	70	4	–	37.4	15			–	–			13
221	994	49 f	ca+	+	+++	–	–	–	10	2	4	3	–	37.1	8			–	–		(3)	14
222	1425	65 m	ca	+++	+++	–	–	1	1	1	5	–	–	37.3	6			–	–			
223	**1515**	**52** f	cc	–	+++	+	–	–	**0**	fr.	–	–	–	**37**	**18**			–	–			**8**
224	1749	44 m	c	+	++	+++	+	3	2	4	20	5	–	38.6	2			–	†			
225	1750	39 m	ca+	–	+++	+	–	–	20	6	–	10	–	37	17			–	–			9
226	1808	33 f	c+	–	+++	–	–	–	1	8	14	5	R+	37.4	8			–	–			
227	1935	42 f	ca	+	+	++	–	3	15	2	8	4	–	39	7			1	–			
228	1980	61 m	ca–	–	++	+	–	–	3	8	45	4	–	38.1	16			–	–			
229	2028	50 f	ca	+	+++	++	–	1	1	1	15	5	–	38.3	18			–	–			
230	2082	30 f	c	–	+++	++	–	–	1	2	12	8	–	38.1	4			2	–			12/17
231	2143	42 f	ca	+	+	+	–	1	1	3	11	5	–	39.4	9			4	–			
232	2161	63 f	ca	+	+	+	–	3	1	1	–	–	–	38.3	–			–	–			21
233	2233	41 f	cc	+	++	+	–	–	5	26	32	10	–	39.5	64			1	–			
234	2273	35 f	ca	+	+++	+	–	1	2	10	7	6	R+	38	13			–	–			
235	2275	39 f	ca+	–	++	++	–	–	1	14	70	3	–	38.4	34			–	–			
236	2298	61 f	ca	–	+++	+	–	1	2	7	–	–	–	37.7	29			2	–			20
237	2405	39 f	ca	++	++	++	+	3	1	15	6	5	–	39.1	83			3	–			
238	2443	38 m	cc	+	+++	–	–	–	7	13	–	5	–	37.3	71			–	–			

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239	2457/46	64 f	c+	+	+++	+	–	–	10	13	–	10	–	39	–			–	–			
240	2475	29 f	ca	–	++	+++	–	1	1	2	6	5	–	37.2	53			1	–			
241	2481	55 f	cc	+	+++	+	–	–	1	13	–	3	–	38.1	–			4	–		5	3
242	2545	60 f	ca	–	+++	+	–	1	15	11	–	5	R+	37.5	–			–	–			
243	2554	36 f	c	–	++	+	–	–	6	6	19	6	–	37.8	9			1	–			
244	2749	53 f	ca	+	+++	–	–	1	1	13	1.33	7	R+	38.1	21			–	–	ca		
245	3654	64 f	cc	+	++	++	–	–	7	7	1.0	6	–	37.8	29	1.6	o	1	–	ca		15
246	3753	67 m	cc+	+++	++	+++	++	–	1	5	1.6	4	R+	37.6	33	0.3	o	–	–	ca		
247	3756	28 m	cc	+	++	–	+	1	10	6	0.7	4	R+	37.7	1	0.2	o	–	–	ca		
248	3855	77 f	c	–	++	+	–	–	10	17	0.6	4	R–	38.2	57	–	–	–	–	–		
249	3923	23 f	c	–	+++	+	–	–	8	6	2.3	3	R+	37.3	23	1.7	o	1	–	c		
250	3959	35 f	ca	+	+++	+++	++	–	8	12	0.7	6	R+	38.5	76	3.3	o	–	–	ca		
251	3978	34 f	c+	–	++	++	+	–	10	6	1.6	4	–	37.8	6	1.0	o	3	–	ca		9
252	3980	60 f	ca	+	+++	+	+	3	5	16	1.8	10	–	38.5	70	0.7	o	3	–	ca	$\frac{4}{5}$	$\frac{4}{15}$
253	3995	50 m	ca	–	+++	+	–	–	16	29	0.6	4	R+	37.6	25	1.8	o	–	–			9
254	4079	55 f	c+	++	+++	+	++	–	8	13	5.65	12	R+	39.7	29	0.7	o	1	–	c	$\frac{7}{5}$	18
255	4092	61 m	ca+	–	++	–	–	3	2	11	4.8	4	R+	39.6	28	0.2	o	–	–	cc		1
256	4127	32 f	ca	–	++	–	+	–	2	10	1.0	5	R+	38.2	33	0.6	++	2	–	ca		8
257	4252	24 f	ca	+	++	+	++	3	2	2	1.38	7	–	39	46	1.6	++	3	–	ca		
258	8/47	48 f	cc	+	++	++	–	–	2	20	7.3	3	R+	37.7	20	1.3	+++	–	–		4	
259	27	47 f	cc	+	+++	–	+	–	3	14	2.1	6	R+	37.6	6	4.2	o	1	–	cc		9
260	119	30 f	ca	–	+++	–	+	1	2	11	0.96	5	R+	38.4	8	0.5	++++	2	–	ca		12
261	430	23 f	c	–	++	+	+	–	20	4	1.5	8	R+	37.7	38	1.1	++	1	–			$\frac{2}{13}$
262	440	26 m	ca	+	+	+	–	3	2	2	2.0	5	–	39.2	24	0.2	++	–	–	ca		
263	502	66 f	ca+	–	+++	–	–	1	10	14	0.75	4	R+	38.9	46	1.1	+	8	–	ca		
264	529	61 f	c	+	+++	+	+	–	1	9	0.5	10	R–	37.8	13	–	–	2	20†	ca	20	
265	604	67 m	ca+	–	+++	+	++	3	20	14	2.1	12	R+	38.3	76	0.7	o	–	–	ca		
266	646	24 f	c	–	++	+++	–	–	3	3	0.4	3	R+	37.5	18	1.0	o	o	–	ca		15
267	651	65 f	cc	+	+++	–	+	1	s.	15	0.9	15	R+	38.4	45	1.3	+	1	–	cp		12
268	668	45 f	cc	–	+++	++	–	–	4	3	8.2	14	R+	39.1	8	0.9	o	3	–	cp		
269	678	48 f	ca	–	++	+	–	1	3	16	0.21	8	R+	37.5	113	0.7	+	o	–	ca		
270	707	62 f	cc+	+	++	++	++	1	2	6	0.64	5	R+	37.1	59	0.5	o	o	–	ca		
271	732	27 f	ca	–	+	++	–	3	s.	4	1.7	5	–	40	16	1.7	++	1	–	ca		$\frac{7}{11}$
272	865	58 m	cc	+	++	++	+	–	30	8	5.4	2	R+	37.3	8	0.7	o	–	–			
273	866	29 f	cc	–	++	–	–	–	25	4	2.4	4	R–	37.3	8	2.5	+	1	–	cp		
274	**880**	**43** f	c	+++	+++	+	–	**1**	**100**	fr.	**0.9**	**3**	R–	**37.4**	**25**	**0.5**	o	**6**	–	ca		
275	918	49 m	ca+	+	+++	+	–	–	10	7	1.0	3	R+	37.6	7	1.2	o	–	–			
276	1020	37 f	ca+	–	+++	+	+	3	10	7	0.21	5	R+	37.8	18	0.4	+++	2	–	ca		12
277	1032	52 f	ca	+	+++	++	++	3	10	11	1.3	6	R+	39.3	27	0.6	++++	3	–	ca		13
278	1080	46 f	cc	+	+	+	–	1	10	4	0.7	7	R+	37.4	13	1.1	o	o	–	ca		12
279	1103	41 f	cc	+	++	+	–	1	100	4	1.5	3	R+	37.4	10	0.7	o	2	–	cc		8
280	1169	20 f	c	–	+++	++	–	–	s.	7	0.8	7	R+	39	24	0.5	o	–	–			
281	1278	41 f	ca	–	+++	+	–	1	1	16	0.26	7	R+	38.6	46	0.6	o	1	–	ca		
282	1279	49 f	cc	–	++	+	–	1	1	20	0.17	6	–	37.8	48	0.5	o	3	–	ca		
283	1309	42 f	cc	–	+++	+++	–	–	50	9	0.67	5	R–	38	32	1.0	++	o	–	c		2
284	1369	44 f	c	+	+++	–	–	–	15	18	0.8	3	–	37.5	12	1.0	o	3	–	c		2
285	1387	60 f	ca	++	+++	++	–	1	1	1	0.75	4	–	38.6	17	1.5	+	4	–	ca	5	1
286	1402	63 f	ca	–	+++	+++	–	3	2	10	1.3		–	38.2	21	0.1	o	2	–	ca		1

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287	1459/47	47 m	ca	–	+++	+	–	1	5	32	0.8	5	R+	37.5	12	0.3	+	–	–	ca		
288	1461	55 f	ca	++	+++	++	+	–	2	9	1.8	5	R+	38.2	12	1.8	++	4	–	ca		
289	1485	50 f	ca	–	+++	++	–	1	3	11	1.2	7	R+	36.8	72	0.6	++	4	–	ca		12
290	1638	34 f	c	–	+++	–	–	–	2	5	0.96	4	R–	37.4	10	0.8	+	3	–	c		
291	1673	57 f	c	–	++	–	–	1	s.	12	0.73		R+	37.5	23	2.9	+++	5	–	c	5	
292	1674	41 f	c	–	+++	+	–	1	1	9	0.83	3	R+	38.1	21	1.0	+	2	–	ca		
293	1810	61 f	c	–	+++	++	–	–	17	10	5.9	4	–	38.2	22	0.2	0	3	–	c		9
294	1828	47 f	ca	+	++	+	+	–	2	8	3.5	5	R+	38	27	0.6	0	–	–			
295	**1925**	**59** f	cc	+	+++	+++	–	**3**	s.	**40**	**1.1**	**5**	–	**38.4**	**60**	**0.2**	**0**	–	–	cc	**5**	**12**
296	2066	54 f	cc	++	+++	+	++	–	8	15	9.5	7	R+	40	6	0.2	++	1	–	ccp		12
297	2298	66 f	cc	+	+++	++	–	–	1	18	2.6	6	R+	39.4	115	0.5	++	–	–	cc		17
298	2342	43 f	ca	+	++	+++	++	3	2	36	1.3	5	R+	37	3	0.7	+	1	–	ca		15
299	2365	69 m	cc	+	+++	+	+	–	50	20	1.4	7	R+	37.6	50	0.9	++	–	–			8
300	2372	37 f	cc	–	+++	–	+	–	1	13	0.6	6	–	38.4	31	1.0	+	5	–	ca		
301	**2449**	**46** f	c	+	+++	++	–	–	1	fr.	2.0	5	–	37.4	22	1.7	++	–	–			
302	2471	40 f	cc	–	+++	–	–	1	1	8	1.5	10	R+	39	35	0.1	+–	1	–	cc		
303	2475	67 m	cc+	–	++	+	++	1	4	15	4.9	8	R+	38.5	29	0.2	+++	–	–	ca		5
304	2532	53 m	ca	–	++	++	+	–	2	3	–	5	–	38.4	7	0.2	0	–	–	ca		8
305	2768	48 m	ca	++	+	+–	–	1	4	10	1.4	6	–	38.3	68	0.8	0	–	–	ca		
306	2801	70 f	cc	+	+++	+	+	–	s.	6	1.3	3	R+	37.6	42	5.8	+–	–	–	ca	5	3
307	2953	43 f	c	+	++	–	++	–	8	18	1.0	5	R+	37.3	20	0.8	+–	0	–	c		
308	2997	52 f	cc	++	–+	+	–	1	5	10	3.0	11	R+	38.4	32	0.7	0	5	–	c		
309	3032	40 f	cc	+	+++	++	–	1	1	8	3.8	6	R+	37.6	11	1.3	+++	5	–	ccp	5	9
310	3052	52 f	cc	++	+++	++	+++	1	30	2	0.59	4	R+	38	45	0.5	0	5	–	ccp		
311	**3217**	**67** f	c	+	+++	+	–	–	**0**	fr.	**0.33**	**9**	R–	**37.6**	**32**	**0.4**	**0**	**1**	–			
312	3279	31 f	ca	–	+++	+	++	1	2	10	1.2	6	R+	38.6	32	0.7	++	3	–	ca		9 13
313	3300	52 f	ca	–	+++	++	+	1	2	18	0.59	5	R+	39.3	70	0.1	0	0	–	ca		17
314	3325	31 f	ca	+	– – –	·	+	·	4	24	1.2	10	R+	38.2	11	0.7	++		–	ca		
315	3356	43 f	ca	+	++	++	–	1	5	12	3.2	4	R+	38.1	6	0.6	+	2	–	ca		
316	3385	71 f	ca	+	++	–	+	1	20	21	2.0	6	–	38.9	22	4.3	+++	2	–	ca	15	
317	3398	60 f	cc	+	++	–	+	–	30	6	0.43	3	–	38.2	3	0.1	0	2	–	ca		14
318	3406	58 m	cc	–	+++	++	–	–	1	11	0.53	4	R+	38.2	68	0.3	0	–	–	cc		
319	3457	40 f	cc	+	+++	+	+++	1	15	19	2.5	6	R+	37.8	16	1.3	+–	2	–	ccp		14
320	3471	46 f	c	+	+++	++	–	1	3	11	3.3	12	R+	38.8	30	0.7	+	–	–	c		3
321	3497	48 f	ca	+	+++	–	++	2	4	9	1.1	5	R+	37.2	36	0	0	2	–	ca		14
322	3501	35 f	cc	–	+++	–	–	1	10	14	1.7	4	R+	37.6	9	0.1	0	4	–	ccp		
323	3518	52 m	c	+	+++	+	+	1	20	8	0.85	2	R+	37.4	9	0.5	+	–	–	ca		
324	3597	49 f	cc	+	+++	+	–	–	10	8	0.52	4	R–	37.8	18	3.6	0	–	–			7 14
325	3799	45 f	cc+	+	++	–	+	–	2	10	5.1	6	R+	37.5	48	2.3	0	1	–	cc		12
326	971	29 f	ca	–	+++	++	–	2	4	14	18	5	R+	37	–	–	–	4	–	ca		1
327	1064	27 f	ca	–	+–	+	–	2	1	4	6	–	–	37.6	–	–	–	3	–	ca		
328	1142	59 f	ca+	+	+	+++	+++	3	1	7	42	5	–	38	–	–	–	–	–	ca		17
329	**3/48**	**57** f	c+	+	+++	++	–	**1**	**5**	fr.	**2.4**	**11**	R+	**38.6**	**21**	**1.8**	++	0	–	cp		
330	56	62 f	ca+	+	+	++	+	1	50	8	25.5	5	–	39.6	92	3.5	0	–	–	ca		
331	66	59 f	ca	+	+++	+	+	1	10	15	2.3	5	R+	38.6	24	2.3	++	2	–			
332	81	50 f	c	+	+++	++	–	–	3	13	0.65	5	R+	37.3	22	1.3	+	2	–	c		
333	102	50 f	c	+	+++	–	++	–	s.	10	0.37	5	R–	37.7	11	1.3	0	0	–	cp		12 13
334	124	62 f	c	–	+++	+	–	–	2	13	3	8	R+	39.5	13	0.7	+	6	–	c		8
335	155	37 f	ca	+	++	+	–	3	1	3	0.91	6	–	38.6	96	0.6	0	4	–	ca		

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336	249/48	40 f	cc	–	++	–	++	1	30	14	0.7	6	R+	37.4	20	0.4	0	2	–	ccp		
337	308	43 f	c	+	+++	+	++	–	8	6	1.0	4	R–	37.1	4	0.8	0	1	–			15
338	342	61 f	ca	+	+++	++	+	1	50	13	0.96	5	–	38	69	0.6	0	4	–	ca	5	5
339	418	55 f	ca	++	+++	++	+	1	1	7	1.3	9	R+	38	18	0.1	++	–	–	ca		7
340	463	55 f	cc	+	++	+	+	–	2	12	5.1	8	R+	38	15	0.3	0	1	–			12
341	562	68 f	ca+	+	+++	+++	–	–	8	25	8.2	4	–	39.6	73	3,8	+++	–	–	ca		
342	599	43 f	cc+	+	+++	+	–	1	1	32	1.0	5	R–	38.2	95	0.9	++	2	–	cc		
343	**676**	**40** f	c	+	+++	–	–	–	**50**	fr.	**0.37**	**4**	R–	**37.8**	**9**	**0.7**	**0**	**3**	–	c		
344	717	53 f	ca	+	+++	+	++	2	18	16	0.6	5	R+	39.3	82	0.3	0	–	–	ca		12
345	**805**	**60** f	c	+	+++	+	–	–	**0**	fr.	**1.1**	–	–	**39**	**17**	–	–	–	–			
346	832	21 f	c	–	+++	+	–	–	10	28	0.75	5	R–	37.4	7	0.7	++	1	–	c		12
347	847	60 f	ca	+	+++	+	+++	1	20	17	0.96	5	R+	38.6	62	0.7	++	3	–	ca		13
348	860	50 f	ca	–	+++	+	+	–	s.	13	1.8	7	R+	38.5	47	0.3	++	–	–	ca		
349	879	52 f	ca	+	+++	++	++	3	15	13	0.69	4	R+	37.3	19	0.7	0	4	–	ca		14
350	917	45 f	ca	+	+++	++	++	1	37	9	1.3	5	R+	37.8	15	2.0	+	1	–	ca		14
351	965	36 f	c	+	++	–	–	–	3	11	1.06	3	R–	37.9	6	0	0	2	–			
352	1039	53 f	cc+	+	+++	++	–	1	11	2	3.6	9	–	40.1	112	0.1	0	0	–			
353	1056	30 f	cc	+	+++	+	++	–	10	11	0.6	5	R–	37.5	32	0.2	0	–	–			12
354	1139	30 f	c	+	+++	+	+	1	2	13	1.1	11	R–	36.5	5	0	++	1	–	cp		
355	1179	61 m	ca	–	++	+++	–	3	1	2	2.1	5	–	39.3	56	0	+	–	–	ca		
356	1806	25 f	cc	–	+++	–	++	–	2	8	1.7	4	R+	37	14	0.9	+	–	–			14
357	2068	49 f	ca+	–	+++	++	–	1	4	11	0.75	5	R+	38.2	18	0.2	+	1	–	ca	15	15 19
358	**2235**	**61** f	cc	+	+++	+	–	**1**	**8**	fr.	**1.3**	6	–	**37.4**	**4**	**0.2**	+++	**3**	–	cc		8 19
359	2250	41 f	c+	+	+++	++	–	–	50	25	3.3	13	–	39.9	16	0.4	0	2	–			
360	2256	54 f	cc	+	+++	+++	++	1	3	11	1.01	7	–	38.2	24	2.7	0	3	–	ca		14 17
361	2309	56 f	c	–	+++	–	–	1	5	16	1.4	14	R–	38.5	28	0.7	+++	–	–	cp		
362	2382	59 f	ca	+	++	++	–	–	5	15	2.05	6	R+	39.6	60	0.2	++	2	–	ca		
363	2465	58 f	cc	++	+++	+	–	–	10	7	0.96	5	R–	38	21	1.0	+++	3	–	c	5	14
364	**2494**	**37** f	cc	–	+++	–	–	1	10	60	0.69	3	–	37.4	6	1.0	+++	2	–	ccp		
365	2547	71 f	ca	–	+	+++	–	3	3	3	1.06	5	–	40	42	0.2	+++	4	–			7 1
366	2549	23 f	ca	+	+++	++	+	1	2	2	1.28	5	–	39	47	0.7	+++	0	–	ca		
367	2621	32 f	c	+	++	–	–	1	30	8	1.2	5	R–	37.4	5	0.2	+++	1	–	c		
368	**2662**	**42** f	cc–	–	+++	+	–	**1**	**0**	fr.	**1.3**	3	R+	**37.2**	7	0.8	+	2	–	cp		12 1
369	3164	26 f	c	+	++	–	–	1	3	12	5.0	5	R+	37.7	31	1.4	++	2	–	c		
370	3189	41 f	c+	–	+	+	+	–	7	13	1.5	11	–	37.2	95	0.8	+	9	–	c		2
371	3197	18 m	c+	+	++	–	–	1	8	13	0.96	10	R–	37.4	7	1.3	+	–	–	c		
372	3296	62 f	ca+	++	++	–	+	2	2	13	0.9	2	R+	38.5	30	0.1	0	–	–	ca	4	
373	3314	44 f	ca	+++	+++	++	+	3	1	13	0.96	11	R+	39.8	–	0.2	0	5	–	ca		
374	3340	53 f	cc+	–	+++	–	–	1	15	12	0.7	4	R+	37.3	8	0.2	0	–	–	cc		7 15
375	3390	30 f	cc+	–	+	–	–	–	1	8	2.7	9	R+	39.3	90	0.5	+++	0	–	cc		
376	**3459**	**55** f	cc–	+	+++	–	–	–	0	fr.	0.7	5	R+	**37.3**	**11**	**0.1**	++	4	–	cc		
377	3511	39 f	ca	–	+++	++	–	1	7	9	1.0	6	R+	38	35	0.6	0	3	–			
378	3513	55 f	cc	+	++	+	–	1	1	5	0.72	7	R+	37.8	11	0.2	–	3	–	cc		
379	3532	52 f	ca+	+	++	++	+	–	4	15	1.8	7	R+	38.6	20	1.9	–	7	–	ca		
380	3566	76 f	cc+	–	++	++	–	–	4	27	17	4	–	37.6	89	0.4	–	3	†	ccp		
381	3658	33 f	cc+	–	+++	–	++	1	2	4	0.74	5	R+	37.6	12	–	–	0	–	cc		
382	3715	61 f	cc	+	+++	+	–	3	3	8	0.75	9	R+	37.8	29	2.2	++	8	–			6
383	3726	50 f	cc+	–	++	+	+	–	4	14	0.85	7	R–	38.7	16	1.6	–	–	–			19
384	3767	47 f	c	+	+++	–	++	–	7	14	1.5	8	–	38.5	95	0.5	–	–	–	c		

No.	Diary No.	Age & Sex	Diagnosis	Fatty inf.	Glyc.	Lymph. inf.	Hepatitis	Gallbl. Cont.	Attacks	Op. day	Meul. s. Bil.	Diastase	Roentg. Result	Temp.	Sed. Rate	Thymol	Hanger	Para	Course	Micr. app. of G.	Sim. Dis.	Prev. Dis.
385	3781/48	55 f	cc+	+	+++	–	–	1	10	21	3.7	6	R+	38.6	23	1.4	–	1	–	cc		9
386	3820	54 f	cc	++	++	–	–	–	4	17	0.32	6	R+	37.7	51	2	–	1	–	ca		1
387	3869	55 f	ca	+++	++	++	–	3	10	6	0.37	7	–	40	102	–	–	–	–	ca		
388	3928	40 f	cc	–	+++	–	–	1	s.	10	1.0	7	R+	37.4	11	1.4	–	–	–	c		
389	3946	47 f	cc	–	+++	++	–	1	4	8	4.5	11	R+	38.5	32	1.0	+	–	–	cc		
390	89/49	41 f	c	–	++	+	–	–	2	16	0.69	3	R+	39	8	0	++	–	–			
391	119	23 f	ca	–	++	–	–	–	4	3	0.59	11	R+	37.8	17	0.5	+	–	–			
392	148	59 f	ca	++	+++	–	–	1	10	1	0.69	5	–	38.2	6	1.3	+++	–	–		5	
393	182	49 m	cc+	–	+++	+++	+	1	3	7	0.96	4	R+	36.8	7	0.9	+	–	–	cc		
394	218	51 m	cc+	–	+++	–	–	–	4	12	1.38	5	–	38.1	51	0.4	+	–	–			12 15
395	615	72 m	cc+	–	+++	++	–	1	4	18	9	9	R+	38.6	74	1.3	++++	2	–	cc	5	3 8 7
396	713	45 f	c	–	+++	–	+	–	100	7	0.27	5	R–	37.5	57	1.2	+++	2	–	cp		19 7
397	866	75 f	ca	+	++	++	–	1	1	4	0.7	6	–	38.2	53	0.3	++	–	–		5	5
398	874	55 f	cc	+	+++	++	+	–	4	5	0.7	5	R+	37,5	27	1.0	++	–	–	ca		13
399	969	61 m	cc+	++	++	++	–	–	3	30	6.3	5	–	37,3	18	0.9	0	–	–	cc		
400	**3337**	**36** f	c	–	+++	–	–	–	**0**	fr.	**0.9**	**5**	R–	**37.5**	**7**	**0.6**	**0**	–	–			

Key.

Diagnosis:

c = cholelithiasis
ca = cholecystitis acuta
cc = cholecystitis chron.
p = phlebitis
– = sine calculis
+ = cum choledocholithiasis
† = dead
fr = free intervall
s = several

Roentgenograhpy:

R– = neg. roentgen
R+ = pos. roentgen

Diseases:

1. Abscess, plegmone, erysipelas, ulcus varicosum
2. Otitis, mastoiditis, sinuitis
3. Goitre (toxic)
4. Diabetes
5. Vitium org. cordis. Myocardit. Hypertonia.
6. Asthma, urticaria
7. Pneumonia, bronchopneumonia
8. Ulcus
9. Gastroenteritis
10. Pancreatitis
11. Ileus
12. Appendicitis. Peritonitis.
13. Hepatitis
14. Salpingitis. Endometritis
15. Cystitis, pyelitis, nefritis
16. Uremia
17. Polyarthritis
18. Abus. ethyl.
19. Migraine
20. Trombosis-embolism
21. Anemia

Gallbladder content:

1. nihil
2. pus sine bacteria
3. pus cum bacteria

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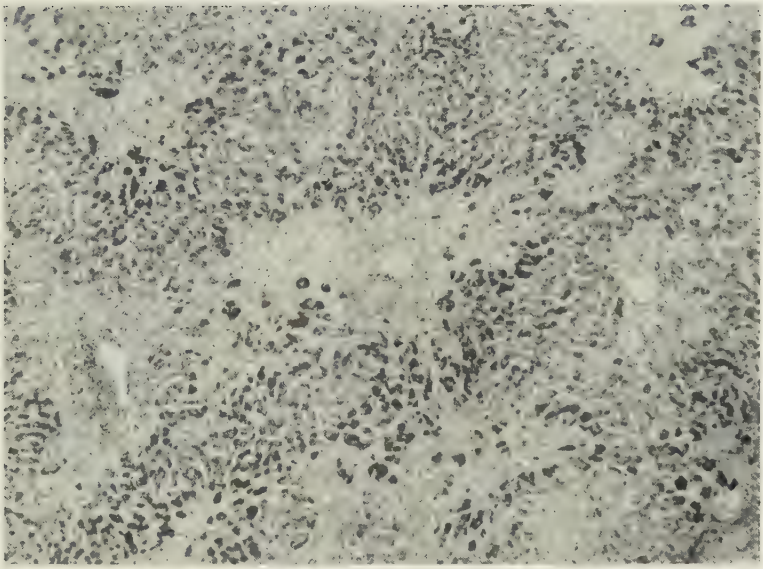

Fig. 13. Survey of viral hepatitis. (U 229/47) Glycogen stain. (50 ×)

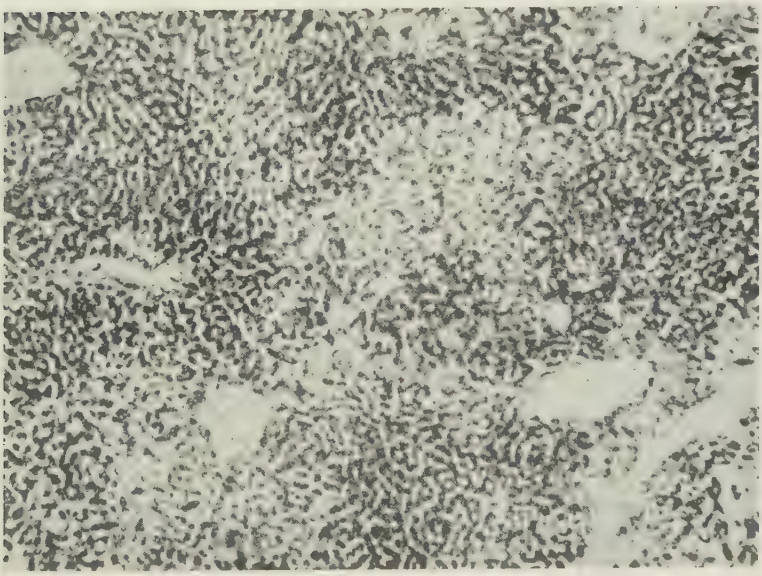

Fig. 14. Survey of toxic hepatitis. Case 310. Glycogen stain. (50 ×)

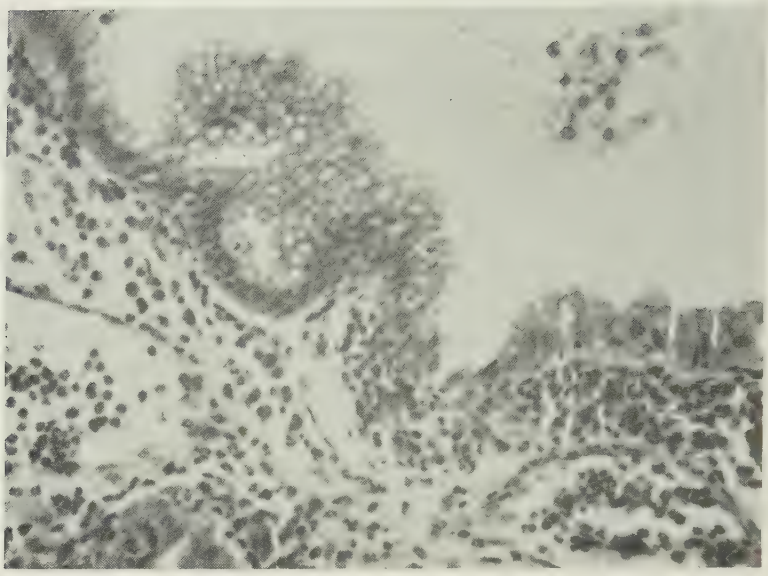

Fig. 15. Detail of gallbladder mucosa with acute inflammation. Case 310. Hematoxylin-Eosin stain. (400 ×)

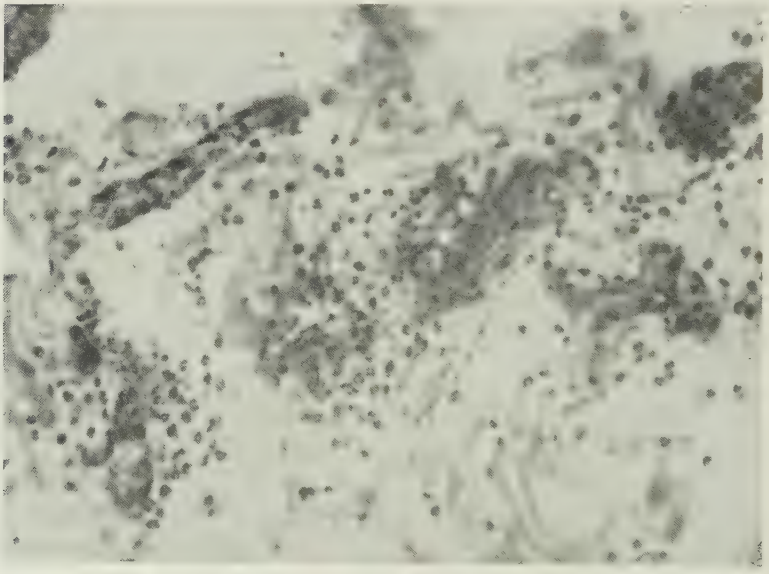

Fig. 16. Detail of gallbladder serosa in cholelithiasis with local inflammation. Case 361. Hematoxylin-Eosin. (400 ×)

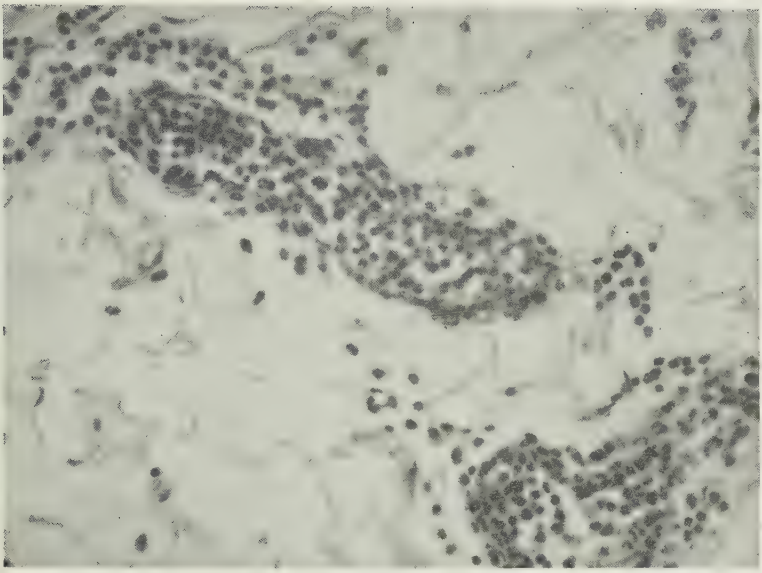

Fig. 17. Detail of gallbladder serosa in cholelithiasis with phlebitis. Case 329. Hematoxylin-Eosin. (400 ×)

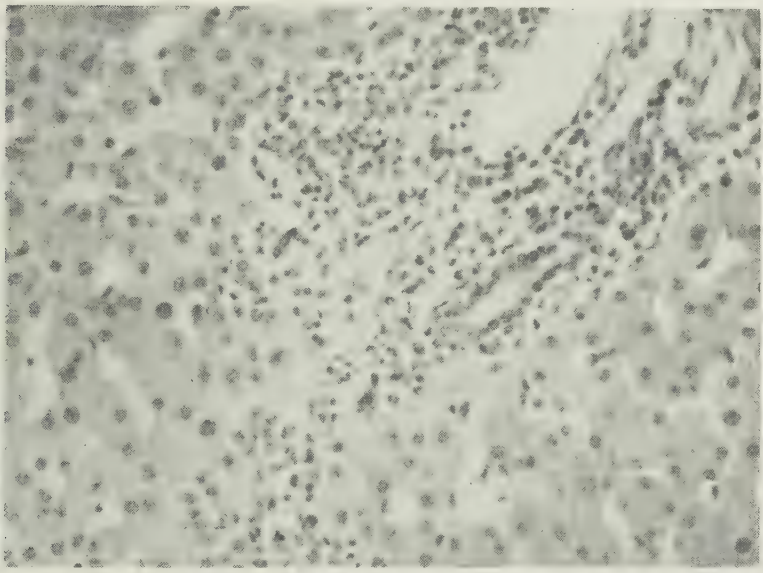

Fig. 18. Early inflammation in the lobular periphery. Leukocyte invasion. Case 304. Hematoxylin-Eosin stain. (400 ×)

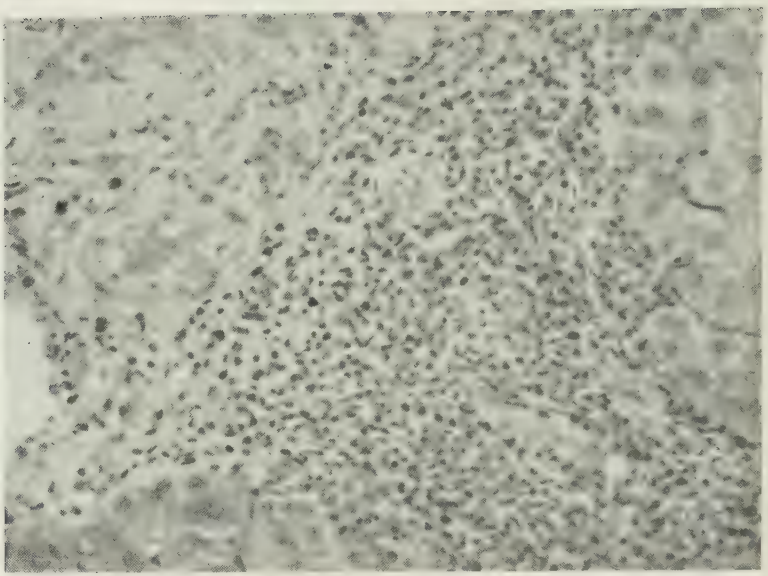

Fig. 19. Leukocyte infiltration in portal cord with bile ducts coaffected. Case 224. Hematoxylin-Eosin. (400 ×)

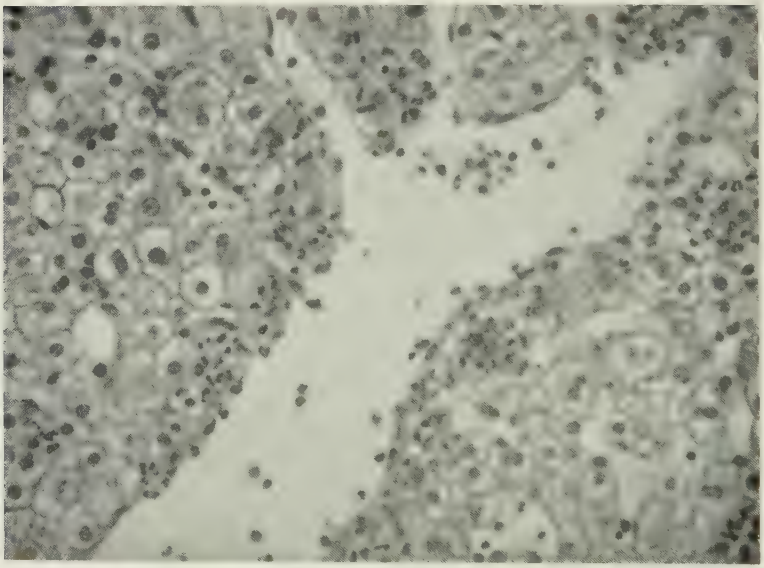

Fig. 20. Toxic hepatitis showing early hepatocellular necrosis around the central vein. Case 319. Hematoxylin-Eosin. (400 ×)

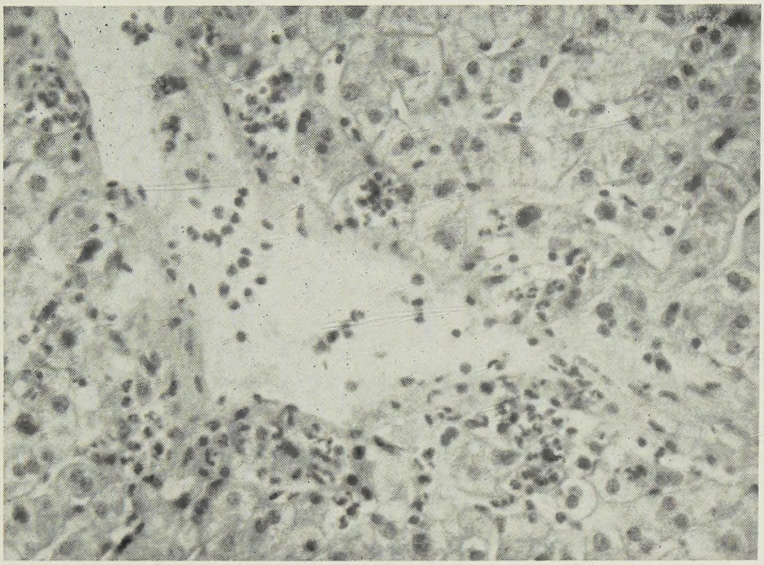

Fig. 21. Toxic hepatitis showing advanced hepatocellular necrosis. Case 310. Hematoxylin-Eosin. (400 ×)

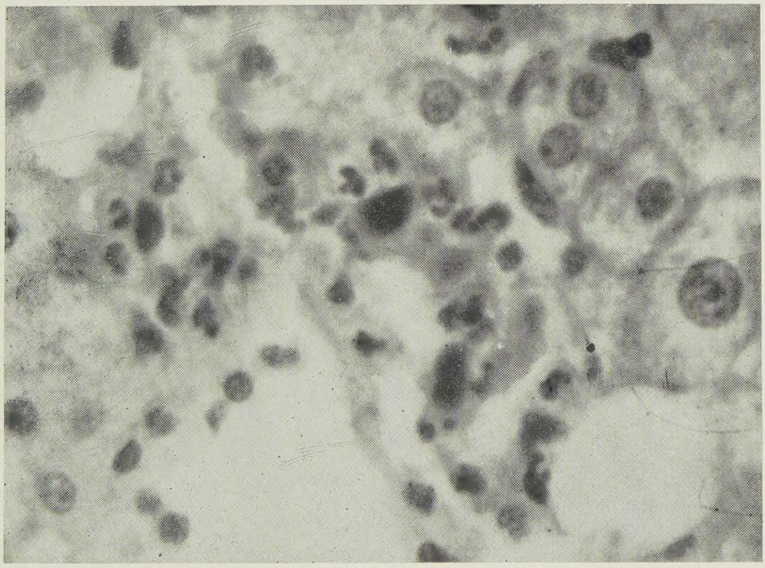

Fig. 22. Absorption of necrotized liver cells. Case 250. Hematoxylin-Eosin. (1 000 ×)

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